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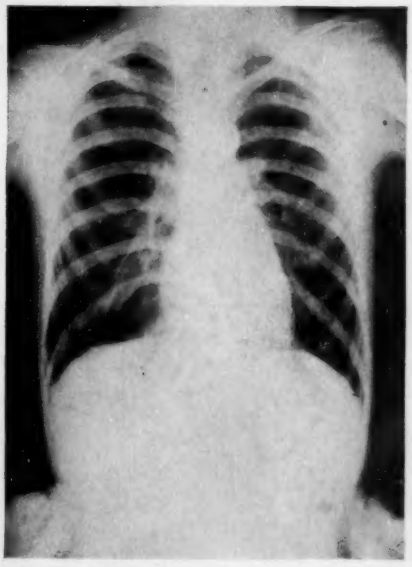

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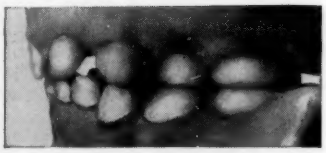

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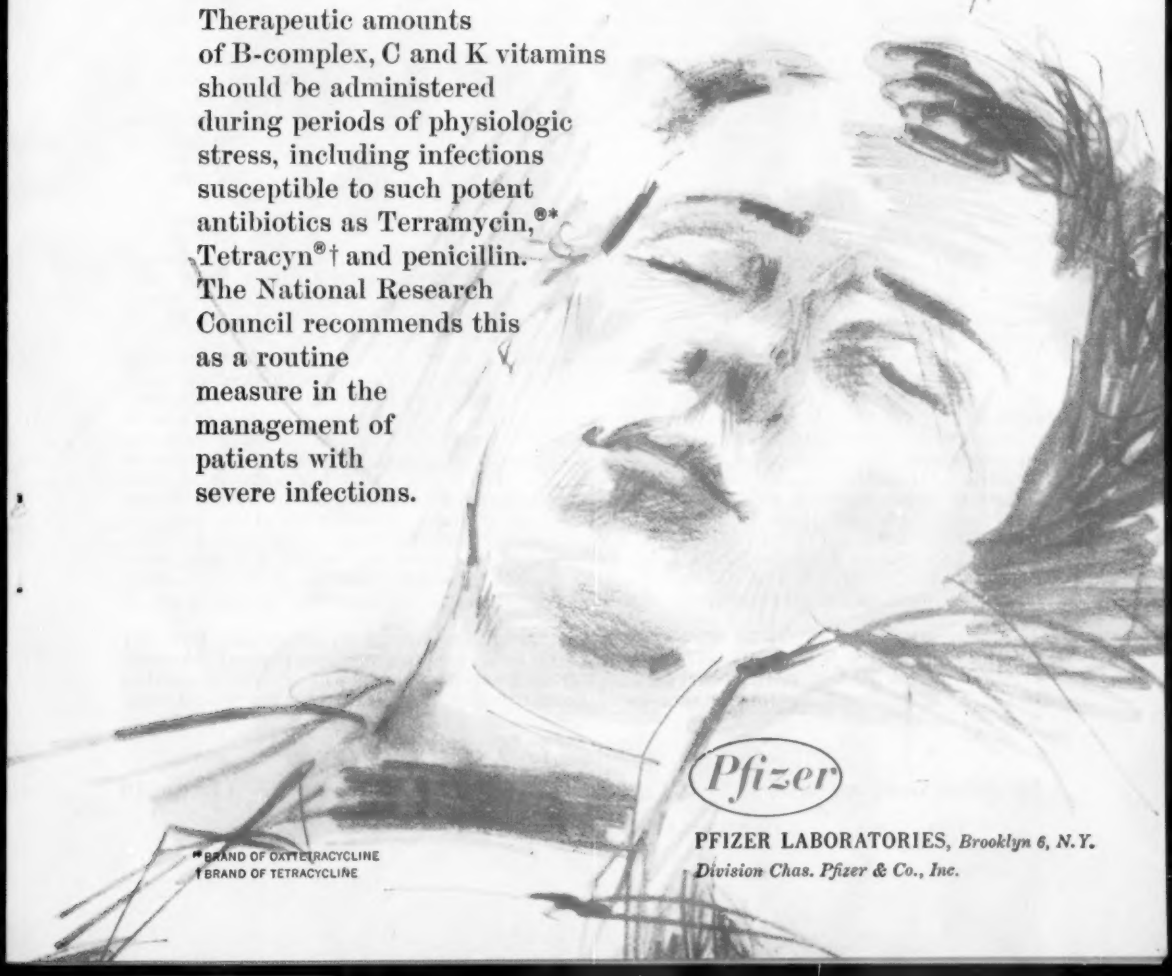

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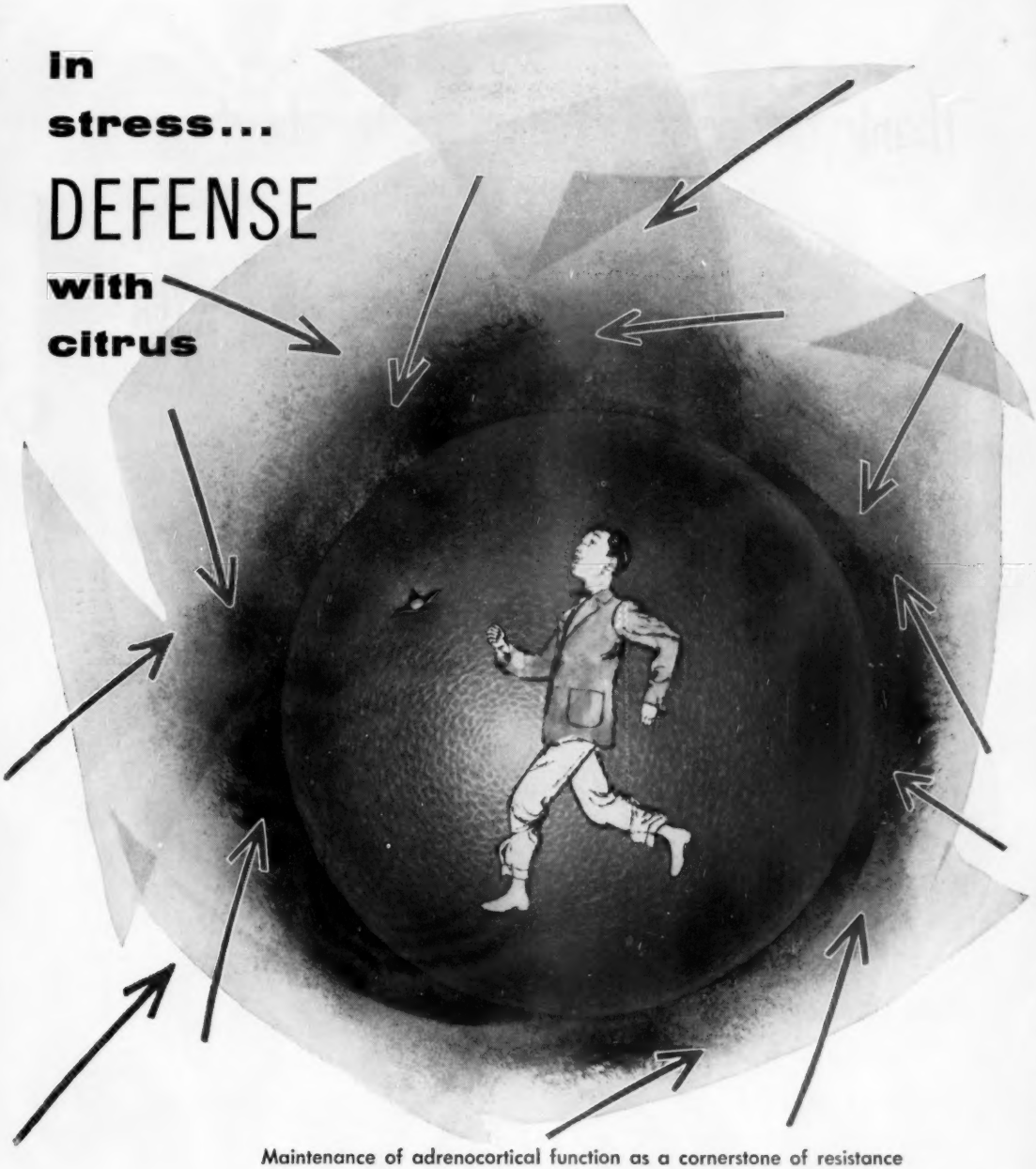

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Oxygen Administration and Retrolental Fibroplasia

MARY ALLEN ENGLE, M.D.
DAVID H. BAKER, M.D.
IRVING BARAS, M.D.
ALAN FREEMOND, M.D.
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and
EDWARD W. NORTON, M.D., New York

The high incidence of retrolental fibroplasia (RLF) in premature infants of low birth weight has led to an intensive search for factors contributing to its pathogenesis. Although it probably is not a new disease,[1] it has been recognized with increasing frequency since 1942, when Terry[2] first described the condition, until now it has become one of the two leading causes in the United States of blindness in children.* The currently high occurrence rate cannot be explained either by the higher survival rate in the low-birth-weight group[3] or by the more concerted search for the condition. It undoubtedly indicates a true rise in incidence of the disease.

The development of efficient incubators in the last 15 years has led to the liberal use of oxygen in the care of premature infants. In many nurseries all small premature infants, regardless of respiratory pattern, are routinely placed in incubators supplied with oxygen. This practice was rendered suspect by Kinsey and Zacharias,[4] in 1949, when they noted the parallel rise in the use of oxygen-enriched incubators in premature nurseries and the appearance of RLF. This correlation spread from this country to many parts of the world as modern incubators and oxygen became more readily available. In 1951, Lelong,[5] with his co-workers in France, and Campbell,[6] of Australia, pointed to hyperoxia as important in the development of RLF. In December, 1951, the report by Szewczyk,[7] of East St. Louis, describing the appearance of retrolental changes on withdrawal of oxygen and reversal of the changes with reinstitution of oxygen therapy, gave further support to the concept that oxygen and RLF were in some way linked. In January, 1952, therefore, a study was undertaken in the premature nursery of The New York Hospital to investigate the role of oxygen in the causation of RLF.

PLAN OF STUDY

All babies with a birth weight of 1650 gm. or less were assigned to Group I and Group II by means of a modified random-sampling technique, which permitted contemporary pairing, at the following ages:

Birth Weight	Assignment to Study
1000 gm. or less	14 days
1001-1361 gm.	7 days
1362-1650 gm.	2 days

To reduce the anticipated hazard of early death, all infants in both groups resided in an oxygen-rich environment up to the assigned age. Group I infants were continued in oxygen until they reached or regained a weight of 1600 gm., according to the established nursery routine. Group II babies were weaned from oxygen at the time of assignment to the study. For both groups, weaning from oxygen was accomplished over a four-day period by reduction of the liter-flow rate by one-third on the first and second days, two-thirds on the third day, and completely on the fourth day. Liter-flow gauges were set at a constant flow rate of 3 liters per min-

From the Departments of Pediatrics and Ophthalmology, The New York Hospital-Cornell Medical Center.

This study was supported in part by grants from the Jaffe Fund for Premature Infants and the Playtex Park Research Institute.

* Kerby, C. E.: Personal communication to the authors, National Society for the Prevention of Blindness, 1954.

ute in the Gordon Armstrong incubators and at 1½ liters per minute in the Isolettes. All vents were closed, and oxygen concentrations were measured daily with an Air Shields analyzer. For Group II infants the incubators served only as heated cribs following withdrawal of oxygen. All babies were removed from the incubators to cribs when they reached a weight of 1600 gm.

Infants were paired not only by weight and type of incubator, but insofar as possible conditions of humidity, temperature control, feeding technique, feeding mixture, vitamins, infusions, transfusions, and antibiotics were comparable for both groups.

Relative humidity was not actually measured, but in the Isolette incubators the control was set at 65%-80%, and in the Gordon Armstrong incubators, the relative humidity, as estimated by a comparison of the wet- and dry-bulb indicators, was 70%-80%. Temperatures, recorded every three hours, were maintained at a slightly subnormal level, between 36.4 and 37 C.

Infants were fed every three hours, and those unable to suck were fed by gavage tube passed for each feeding. The feeding mixture was a partially skimmed cow's milk preparation (Alacta) reinforced with Dextri-Maltose. Evaporated milk, six to seven times in 24 hours, replaced the half-skimmed milk mixtures preparatory to discharge. Vitamin K, 4 mg., was given on admission to the nursery, and vitamins A, D, and C were started at the age of one week. They were supplied in a water-miscible form in daily dosages of 10,000 I. U., 1000 I. U., and 50 mg., respectively.

Subcutaneous infusions of a hypotonic salt solution were given two or three times daily during the first week or more of life for dehydration or for oral fluid intake of less than 100 cc. per kilogram by the fourth or fifth day. In general, the smaller the infant the greater was the need for infusions. Transfusions were administered if the hemoglobin level, measured spectrophotometrically, dropped below 8.0-8.5 gm. per 100 cc. and the baby appeared less vigorous than formerly. Here again, the smallest infants were most in need of transfusions. Iron preparations were withheld during residence in the nursery.

Antibiotics were used for treatment of infections, as prophylaxis during the first 48-72 hours for infants transferred from outside hospitals, and for some babies who were receiving frequent clyses for prolonged periods. Aqueous crystalline penicillin, 10,000 units, and streptomycin, 10 mg. per kilogram, each twice daily, were the antibiotics for prophylaxis.

Babies were discharged from the premature nursery when they reached a weight of 2300 gm.

While in the nursery, funduscopic examinations were performed under 2% homatropine and 10% phenylephrine mydriasis at weekly intervals beginning just prior to or at the time of withdrawal from oxygen. Following discharge, the fundi were examined regularly up to 4 or 5 months of age in normal infants or until the eyes which had shown active RLF returned to normal or reached a cicatricial stage (around 6 months of age). The classification of the different stages of the disease followed that recommended by the National Committee on Retrolental Fibroplasia.[8]

The study was begun on Jan. 28, 1952. Infants were assigned for the next 18 months, and the follow-up period extended for an additional 6 months. The study was terminated when this hospital entered the Cooperative Study on the Role of Environmental Oxygen in the Development of RLF.

RESULTS OF STUDY

I. The Role of Oxygen

Ninety-nine infants, 49 boys and 50 girls, reached the age for assignment to the study and were distributed as follows:

Birth Weight	Group I	Group II
1000 gm. and less	5	4
1001-1361 gm.	21	23
1362-1650 gm.	24	22
	50	49

Of the 49 babies originally assigned to Group II, two infants, weighing at birth 1420 and 1580 gm., did not complete the scheduled oxygen reduction because of their poor condition at 2 days of age, and five, all under 1000 gm. when admitted to the study, were either kept in or returned to oxygen because of respiratory difficulty. These seven infants were then maintained in oxygen until a weight of 1600 gm. was attained. They are hereafter referred to as Group II → I and those remaining in the original Group II as II'.

Only one death occurred; a Group II infant with a birth weight of 1190 gm. died on the 11th day of life before oxygen reduction was complete. Four infants, all in the largest weight division, two each in Groups I and II, were lost to follow-up at the age of 6 weeks. At that time, three had normal fundi and the fourth had Stage 1 of active disease in one eye. These five infants were excluded, and the results of the study refer to the 94 surviving infants whose follow-up was adequate.

In this and subsequent tabulations, all stages of active disease (Stages 1-5, from the

mildest to the most severe form) are included under the heading "Active," while all cicatricial changes, Stages A through E, in order of increasing severity, are classified under the heading "Residual." [8] In addition, blindness in one or both eyes (Stages D or E of cicatricial RLF) is tabulated separately under the column "Blind."

significant effect on the incidence of the disease,[9] data on all the babies are combined in Table 2.

There was, therefore, no reduction in total incidence of active or residual RLF with curtailment of oxygen administration by one-third to one-fourth for approximately half of the babies.

TABLE 1.—*Incidence of RLF by Birth Weight*

Birth Weight, Gm.	Infants	Active		Residual		Blind	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
1000 and less	9	8	88.9	3	33.3	1	11.1
1001-1361	43	28	65.1	11	25.6	4	9.3
1362-1650	42	23	54.7	7	16.6	2	4.8
Totals	94	59	62.8	21	22.6	7	7.45

TABLE 2.—*Nursery Incidence of RLF Prior to Present Study (1948 and 1949)*

Birth Weight, Gm.	Infants	Active		Residual		Blind	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
1000 and less	22	22	100	3	13.6	1	4.5
1001-1361	60	42	70	16	26.6	9	15
1362-1650	70	32	45.7	14	20	4	5.7
Totals	152	96	63.2	33	21.7	14	9.2

TABLE 3.—*Relative Incidence of RLF in the Three Groups of the Present Study According to Birth Weight*

Birth Weight, Gm.	I				II′				II → I			
	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
1000 and less	5	4	2	1	1	1	1	0	3	3	0	0
1001-1361	21	14	6	2	20	12	4	1	2	2	1	1
1362-1650	22	13	4	1	18	8	1	0	2	2	2	1
Totals	48	31	12	4	39	21	6	1	7	7	3	2
Per cents	..	64.6	25	8.3	..	53.9	15.4	2.6	..	100	42.9	28.6

The incidence of active and healed RLF was as shown in Table 1.

These results closely paralleled those obtained in a previous study of 152 infants at this hospital during the two years preceding the present study (1948 and 1949).† The oxygen regimen for these 152 infants was similar to that of Group I of the present study except that the flow rate of oxygen was often higher and the oxygen concentration was not measured. Some infants received vitamin E and others corticotropin (ACTH), but, since neither of these agents had any

The relative incidence of RLF in the three groups of the present study is shown according to birth weight in Table 3.

Interpretation of the results is complicated by Group II → I, in which the highest incidence of active and serious residual RLF occurred. The seven infants in this group cannot fairly be included in either Group I or II, since they were originally assigned to Group II but they were subsequently exposed to oxygen for periods comparable to Group I. Nor is it appropriate to subtract them from Group II and consider them separately; those remaining in Group II′ are not then strictly comparable to Group I.

† The New York Hospital: Unpublished data.

TABLE 4.—*Predicted Need for Prolonged Oxygen Therapy (Retrospective Review)*

Birth Weight, Gm.	Group I	Group II	Group II → I
1000 and less	3	0	2
1001-1361	5	2	2
1362-1650	0	0	2
	8	8	

Two possible solutions to resolve this dilemma were proposed by the statistician. Both solutions stem from the assumption that with random assignment to the two matched groups there existed within Group I a set of premature infants who would not have been able to come out of oxygen early in such precarious condition at birth or in the early neonatal period as to preclude early removal from oxygen. The scheduled assignments of these 16 infants turned out to be equally divided between Group I and II. They included six of the seven infants originally assigned to Group II and subsequently shifted to Group II → I because of their need for more prolonged oxygen therapy (Table 4). Despite the difficulties inherent in such a retrospective and subjective analysis, the correlation between prediction and subsequent need for oxygen renders the assumption valid that the proportions of "poor risk" infants in Groups I and II were comparable.

TABLE 5.—*Incidence of RLF in Curtailed and Prolonged Oxygen Groups—"Poor Risk" Patients Removed from Each Group*

	Group I', Prolonged				Group II', Curtailed			
Birth Weight, Gm.	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
1000 and less	2	1	0	0	1	1	1	0
1001-1361	16	11	5	1	20	12	4	1
1362-1650	22	13	4	1	18	8	1	0
Totals	40	25	9	2	39	21	6	1
Per cents	..	62.5	22.5	5.0	..	53.9	15.4	2.6

TABLE 6.—*Incidence of RLF in "Poor Risk" Patients*

	Group I				Group II → I			
Birth Weight, Gm.	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
1000 and less	3	1	1	1	3	3	0	0
1001-1361	5	3	1	1	2	2	1	1
1362-1650	0	0	0	0	2	2	2	1
Totals	8	4	2	2	7	7	3	2

had they been subjected to the test, comparable to the seven in Group II → I.

The first verification of this assumption consisted of a retrospective study of the records of all babies in an attempt to cull from Group I those who might not have tolerated early removal from oxygen. Accordingly, the head nurse in the premature nursery, who was skilled by years of experience in evaluating the condition of premature infants and who did not know the results of the eye examinations, was asked to review the records of the birth histories and immediate neonatal periods of all the babies assigned to the study. She selected 16 babies as being

Excluding these 8 babies from Group I, the remaining 40 infants in Group I' may be compared with the 39 infants in Group II' (Table 5). Differences between Groups I' and II' are not significant.

Of equal interest is the similar incidence of serious RLF and blindness in the eight babies separated in this subjective manner from Group I and in the seven actually separated from Group II (Table 6). This suggested association between "poor prognosis" in the neonatal period and the development of RLF will be considered in more detail in Part II of this paper.

The second calculation proposed by the statistician was also based on the assumption that with matched groups there existed within Group I "poor risk" babies comparable to those in Group II → I. Therefore, since the results on the Group II → I babies were taken out of Group II, these same results, given in Table 3, were also subtracted from each of the columns in the appropriate weight division of the Group I figures, leaving Group I″ for comparison with Group II′. This technique, which avoids the subjective and retrospective analysis above, yielded the information in Table 7. The differences between I″ and II′ are again not statistically significant.

One additional analysis confirmed the above interpretations. Since the infants were admitted to the study by random pairs, the results of both members of the pair were discarded if the results of one member were invalidated, as in the Group II → I infants, or by death of one member of the pair or the loss of one member due to inadequate follow-up. There remained 37 pairs for comparison (Table 8). There is no significant difference between these paired infants in oxygen for curtailed or prolonged periods.

The over-all data establish that curtailed exposure to oxygen as carried out in this study is not accompanied by a reduced incidence of active or cicatricial RLF. More detailed analyses were then made to ascertain if a harmful effect of oxygen were being masked or if other factors equal to or more important than oxygen were operative in the production of RLF.

To investigate the possibility that the harmful role of oxygen was not brought into proper focus by the design or implementation of this study, the following analyses were undertaken.

A. Duration of Oxygen Exposure.—Table 9 shows the total duration of oxygen therapy in the three groups according to birth weight. Only one infant with a birth weight below 1000 gm. in Group II′ was successfully re-

TABLE 7.—*Incidence of RLF in Curtailed and Prolonged Oxygen Therapy Groups*

Results of Group II → I Subtracted from Each Group

	I″, Prolonged				II′, Curtailed			
Birth Weight, Gm.	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
1000 or less.....	2	2*	2	1	1	1	1	0
1001-1361	19	12	5	1	20	12	4	1
1362-1650	20	11	2	0	18	8	1	0
Totals.....	41	25	9	2	39	21	6	1
Per cents.....	..	61.0	21.9	4.9	..	53.9	15.4	2.6

* Subtraction of the Group II → I results for the smallest infants, where there were 3 babies all with active disease but without residual changes from those observed in Group I for this weight level, would leave the inconsistent finding of 1 more patient with residual disease than with active disease. To avoid this contradiction the figure 2 is used for the number with active disease rather than the actual number, 1.

TABLE 8.—*Incidence of RLF in Paired Infants of Curtailed and Prolonged Oxygen Therapy Groups*

	I				II			
Birth Weight, Gm.	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
1000 or less.....	1	1	1	1	1	1	1	0
1001-1361	19	12	4	1	19	11	4	1
1362-1650	17	9	3	1	17	7	1	0
Totals.....	37	22	8	3	37	19	6	1
Per cents.....	..	59.5	21.6	8.1	..	51.4	16.2	2.7

TABLE 9.—*Days of Oxygen Exposure*

Birth Weight, Gm.	Group II′	Group I Average*	Group I Range	Group II → I Average	Group II → I Range
1000 and less..	17	48.6	47-60	55.6	53-60
1001-1361	10	33.3	16-52	45	21-81
1362-1650	5	17.5	8-35	23	20-29

* In this and subsequent Tables, the average is the arithmetical mean.

moved from oxygen in 17 days according to schedule. In the two larger weight divisions, duration of oxygen exposure for Group II' was approximately one-third to one-fourth that for Groups I and II → I.

When the incidence of RLF was tabulated according to the duration of oxygen therapy, it was observed that serious residual RLF occurred more frequently among the 51 babies who were in oxygen for periods longer than two weeks than in the 43 babies who were in oxygen for two weeks or less (Table 10). Moreover, the average duration of oxygen therapy paralleled the development and severity of RLF in infants, if birth weight were disregarded (Table 11). However, when birth weight was considered, the results were quite different (Table 12). Within each weight group the duration of oxygen therapy in infants without and with active RLF are essentially similar (first two columns of Table 12). Nevertheless, those with more serious disease, which ended with scarring or blindness, were in oxygen longer periods than those without retrolental changes. This may indicate that exposure to oxygen does not determine susceptibility to RLF but may influence the severity of the disease once it develops. While this explanation is possible, the observed differences in incidence of the active disease with varying period of oxygen therapy are probably explicable solely on the basis of birth weight and poor neonatal condition.

B. Oxygen Concentrations.—The effect of variations in oxygen concentration was next examined. Measurements in the incubator gave average values above 50% for 14 infants; between 40% and 50% for 52, and below 40% for 28 babies. The development of RLF in each weight division at these concentrations is shown in Table 13. The difference observed in the incidence of RLF at the three different levels of oxygen concentration was not significant.

The occurrence of RLF at these three levels of oxygen concentration for different periods of time is shown in Table 14. Only one set of babies had less than the expected incidence of RLF; at low oxygen concentrations of under 40% for less than a week, five of seven babies in the largest weight division did not develop RLF and the other two had only minor changes which disappeared.

The failure to demonstrate important differences in the incidence of RLF at the levels of oxygen concentrations employed in this study does not establish on the one hand the potentially harmful effects of higher concentrations (70% to 80%) or the potentially beneficial effects of lower concentrations (20% and less) on the other hand. All that may be stated is that low or moderate concentrations of oxygen (less than 40% to greater than 50%) did not substantially reduce the incidence of RLF among premature infants of low birth weight.

C. Time Relation Between Cessation of Oxygen Administration and the Onset of RLF.—Of the 59 infants who developed

TABLE 10.—*Duration of Oxygen Therapy*

		Active		Residual		Blind	
	Infants	No.	Per Cent	No.	Per Cent	No.	Per Cent
Less than 2 wk.....	43	23	53.5	5	11.6	1	2.3
More than 2 wk.....	51	36	61	16	31.3	6	11.6

TABLE 11.—*Days of Oxygen Therapy*

	No Disease	Disease		
		Active	Residual	Blind
No. of infants..	35	59	21	7
Average.....	16.8	23.8	27.9	41.1
Range.....	5-52	5-81	5-81	10-81

TABLE 12.—*Average Days of Oxygen Therapy According to Birth Weight*

Birth Weight, Gm.	No Disease	Disease		
		Active	Residual	Blind
1000 and less.....	47	49.9	40	56
1001-1361.....	20.1	24.9	30	45.5
1362-1650.....	12.8	13.4	19.3	25

active disease, 27 had normal fundi when first examined but showed retrolental changes from one to six weeks after oxygen was stopped. Abnormalities appeared in 12 infants within two weeks following cessation of oxygen administration and by three weeks in another 8 infants. In the seven remaining, was noted (57, 41, and 36 for the three weight groups, respectively) closely approximated the days of life (51, 43, and 33) given by Fletcher [10] for babies of comparable weights to undergo the necessary transformations from an immature to a transitional to a mature fundus susceptible to retrolental

TABLE 13.—*Relationship of Concentration of Oxygen and Birth Weight to RLF*

	Under 40% RLF				40%-50% RLF				Over 50% RLF			
Birth Weight, Gm.	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
1000 and less.....	3	3	1	1	6	5	2	0	0	0	0	0
1001-1361	13	8	3	1	28	19	17	3	2	1	1	0
1362-1650	12	6	1	1	18	10	5	1	12	7	1	0
Totals.....	28	17	5	3	52	34	14	4	14	8	2	0
Per cents.....	..	60.6	14.3	10.7	..	65.4	26.9	7.7	..	57.2	14.3	0

TABLE 14.—*Relationship of Concentration and Duration of Oxygen Therapy to RLF*

	Under 40%				40%-50%				Over 50%			
Duration of Oxygen Therapy	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
Less than 1 wk.....	7	2	0	0	4	3	1	0	6	3	0	0
8-14 days	8	5	3	1	16	9	1	0	2	1	0	0
15-21 days	7	5	0	0	7	5	4	1	4	3	1	0
22-28 days	0	0	0	0	6	3	2	0	1	1	1	0
29-35 days	1	1	1	1	6	4	1	0	1	0	0	0
36-42 days	1	1	0	0	4	3	2	1	0	0	0	0
43-49 days	0	0	0	0	4	2	1	0	0	0	0	0
50-56 days	3	2	1	1	3	3	1	1	0	0	0	0
57-63 days	1	1	0	0	1	1	0	0	0	0	0	0
More than 64 days....	0	0	0	0	1	1	1	1	0	0	0	0
Totals.....	28	17	5	3	52	34	14	4	14	8	2	0
Per cents.....	..	60.6	14.3	10.7	..	65.4	26.9	7.7	..	57.2	14.3	0

TABLE 15.—*Day of Appearance of Eye Changes Subsequent to Withdrawal from Oxygen*

		Days in Oxygen		Day When RLF First Found		Interval After Oxygen Stopped	
Birth Weight, Gm.	Infants	Average	Range	Average	Range	Average	Range
1000 and less.....	3	42.6	16-60	56.7	27-80	11.7	11-14
1001-1361	15	20.4	8-44	40.7	19-64	19.6	8-39
1362-1650	9	14.4	5-19	35.7	16-48	21.2	11-34
Totals.....	27	25.8	.....	44.3	.....	17.5	.....

the changes developed from four to six weeks after supplementary oxygen was terminated. In general, babies in oxygen for the shorter periods (Group II) had an earlier appearance of RLF than did the Group I or II → I children (Table 15).

It is of especial interest that the average day of life at which the first evidence of RLF disease. The observed times of onset of RLF may therefore be related as much to the degree of immaturity of the fundus at birth as to oxygen administration per se.

The observed interval of two to three weeks between appearances of RLF and withdrawal of oxygen, whether done early or late, may represent a time lag before the

reaction of ocular tissues accustomed to an oxygen-enriched environment becomes manifest.[11] That this explanation does not always hold, though, for the development of RLF is shown by the fact that in 11 infants the retrolental changes preceded the discontinuance of oxygen (Table 16). In keeping with the possibility that the time of appearance of the eye changes is explicable on the degree of maturity of the fundus at birth, as was considered for the 27 babies whose ocular changes followed oxygen withdrawal, it is noteworthy that in these 11 babies whose ration of the fundus at birth, but in the absence of accurate estimates which were not made in this study, the results can only be interpreted as lending corroboratory support to Fletcher's concept that the fundus in its immature and transitional stages of development is most susceptible to RLF and that the retrolental changes appear only with the passage of time as the fundus matures. More will be said of this later.

II. Role of Factors Other Than Oxygen

Since the above data did not provide a clear answer to the role of oxygen therapy

Table 16.—*Eye Changes Prior to Withdrawal of Oxygen*

Birth Weight, Gm.	Infants	Days in Oxygen		Age When RLF First Found	
		Average	Range	Average	Range
1000 and less	4	55.8	53-60	31.8	13-60
1001-1361	6	39	16-81	36.7	13-43
1362-1650	1	16	16	16	16
Totals	11	36.9	.....	28.2	.....

Table 17.—*Comparison of Incidence of RLF Observed with That Expected on Basis of Birth Weight*

	Group I				Group II′				Group II → I			
	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
Observed	48	31	12	4	39	21	6	1	7	7	3	2
Expected	..	30.2	10.7	3.6	..	23.8	8.5	2.8	..	5.1	1.8	0.6
Obs.-Exp.	..	0.8	1.3	0.4	..	−2.8	−2.5	−1.8	..	1.9	1.2	1.4
$\frac{(\text{Obs.-Exp.})^2}{\text{Exp.}}$	..	0.021	0.157	0.044	..	0.329	0.735	1.157	..	0.708	0.800	3.266

changes preceded oxygen reduction, the average age for appearance of RLF, 28 days, is comparable to the age 31 days given by Fletcher[10] as the average time it takes for fundi that are at birth transitional in their development to mature and then show RLF.

The remaining 20 infants with RLF were first examined within a few days after oxygen was stopped and were already found to have evidence of the disease on this funduscopic examination. In them it is impossible to determine the relationship, if any, between eye changes and oxygen withdrawal.

As previously implied, the inconstant time relationships between the appearance of the disease and the cessation of oxygen therapy suggest the importance of the stage of maturation of the fundus at birth, but in the absence of accurate estimates which were not made in this study, the results can only be interpreted as lending corroboratory support to Fletcher's concept that the fundus in its immature and transitional stages of development is most susceptible to RLF and that the retrolental changes appear only with the passage of time as the fundus matures. More will be said of this later.

II. Role of Factors Other Than Oxygen

Since the above data did not provide a clear answer to the role of oxygen therapy in this important disease, other accessory factors were investigated.

A. Birth Weight.—The importance of birth weight as a determinant of the development of RLF is shown by a comparison of the observed incidence of RLF in Groups I, II′, and II → I (Table 3) and that expected on the basis of the nursery incidence of the disease at the three weight levels shown in Table 1. The expected incidence was calculated by applying to the number of babies in the three groups at each weight level the appropriate incidence percentage for active and residual disease and blindness. For example, the expected number of babies with active disease among the 48 in Group I was determined by addition of the results obtained from multiplying the number of babies at

each weight level (5, 21, and 22 from the smallest to the largest) by the percentage incidence of active disease at that weight level (88.9%, 65.1%, and 54.8%, respectively). Thus 5 (88.9%) + 21 (65.1%) + 22 (54.8%) = 30.2 babies expected to develop active RLF in Group I. The results of the comparison of the observed and expected incidence are shown in Table 17.

The χ^2's were then calculated by adding the quantities

$$\frac{(\text{Observed}-\text{Expected})^2}{\text{Expected}}$$

for Groups I, II′, and II → I.

Condition	χ^2	Conclusion
Active RLF	1.058	Not significant
Residual RLF	1.692	Not significant
Blindness	4.467	Borderline

The χ^2 for blindness is of borderline significance. The large χ^2 is due to the two cases of blindness in Group II → I instead of the predicted 0.6. There was no apparent excess in Group I, though, where it should occur if oxygen were implicated.

TABLE 18.—*Comparison of Expected and Observed Incidence of RLF in Group II (Combined II′ and II → I)*

	Infants	Active	Residual	Blind
Observed	46	28	9	3
Expected	46	28.9	10.3	3.4

When the results of the babies in Group II → I were combined with those remaining in Group II′ to restore Group II to its original composition, it is seen that here too the observed incidence of retrolental disease did not differ from that expected on the basis of birth weight (Table 18).

The absence of significant differences in the curtailed and prolonged oxygen groups would indicate that the data obtained in this study could be explained by the variation in incidence at each birth weight and that it is unnecessary to assume that oxygen produced additional bad effects.

B. Gestational Age.—In line with the above observations on birth weight, the influence of immaturity as estimated by gestational age was also explored. Despite possible inaccuracies in the determination of gestational age, the duration of pregnancy was calculated for 93 infants whose mothers knew the dates of their last menstrual periods. Birth weights and gestational ages were generally in good agreement. In babies whose birth weights ranged between 800 and 1650 gm., gestational ages ranged from 25 weeks (birth weight 800 gm.) to 40 weeks (a 1620 gm. baby whose mother was seriously ill and died of Hodgkin's disease two weeks after delivery). Forty-two babies had an estimated gestational age of 30 weeks or less, and in 51 the pregnancy lasted for 31 weeks or longer. The occurrence of residual RLF, including blindness, was higher in the first group (Table 19).

Particularly striking was the high incidence of serious RLF ending in residual disease and blindness among the babies born at 29 or 30 weeks of gestation. Of 24 babies in this group, 15 had active RLF, 13 had residual disease, and 6 were blind. In the two babies whose disease regressed, the changes had advanced to Stage 3 bilaterally (based on a scale of 0 to 5 in severity [8]) before improvement occurred. This small group accounted for 62% of all cicatricial RLF and 86% of blindness. At 30 weeks of gestational age, the picture was most severe; 10 of 13 infants had active disease; 8 had residua, and 5 were blind. If a susceptible group can be defined, this would seem to be it.

More immature babies, of 28 weeks' gestation or less, had the highest incidence of vascular changes in the eyegrounds (13 of 18 infants), but only 2 of 18 infants had residual changes, and these were mild (Grade A bilaterally in both, with a severity scale of A to E, where A means mild temporal traction [8]). More mature infants, of 31 weeks' gestation or longer, often showed mild vascular changes (usually Stage 1 or 2), but only 5 of 51 advanced to Stage 3 or had residual changes. One of these reached Stage D in one eye. These data are summarized in Table 20.

It is of interest in this connection that the only baby with a birth weight below 1000

gm. who showed no evidence of RLF was a 950 gm. girl born after a 32-week pregnancy. She was probably more mature than her birth weight would indicate.

The behavior of twins further illustrates the importance of gestational age and fundal maturity. In the total group of 94 babies there were one or both members of 17 sets of twins and 1 of triplets. With 2 exceptions among the 12 sets where both survived, the twins behaved alike with respect not only to the presence or absence of RLF, but also to its severity. For example, exposure to oxygen of one member each of two sets of twins for 10 days in contrast to 50 and 26 days for their mates resulted in identical syndromes with respect to time of development of the active disease and progression to serious RLF with residual scarring. One member of each set was blind in one eye, and their mates had impaired vision.

The exceptions were of a minor nature: the presence of Stage 1 vascular changes in two babies and absence in their mates and the complete regression of changes in one twin whose mate was left with bilateral mild residua. One of two survivors in a set of triplets, exposed to oxygen for 22 days, progressed to Stage 3 of bilateral active disease and to scarring with mild temporal traction in one eye, while his mate, in oxygen for 16 days, had normal fundi.

The high incidence of RLF in five sets of twins born at 30 weeks or less of gestation further points to the significance of this period of fetal life in the development of eye disturbances. Survivors showed active disease with residual changes in four sets and blindness in two. In contrast, in 12 pairs with a gestational age of 31 weeks or greater, two sets showed active and residual disease; four other sets developed Stage 1 changes that regressed, and six pairs had normal fundi throughout.

The race of the infant was unrelated to the incidence of active RLF, but it may have influenced the severity of the disease. Of 11 Negro infants, 7 (63%) had active RLF. However, none progressed to the residual stage. The failure of this small number of Negro babies to develop severe RLF is additional presumptive evidence of the importance of fundal maturity, since Negro babies per unit of body weight are more mature than white children.

The observations on twins and Negro infants support the impression obtained from the study group as a whole that the maturity of the infant at birth and, therefore, the stage of fundal development seem to be crucial pathogenetic factors and may serve as the common denominator upon which a number of extraneous factors may be superimposed.

TABLE 19.—*Influence of Gestational Age on Incidence of RLF*

		RLF					
		Active		Residual		Blind	
Gestational Age	Infants	No.	Per Cent	No.	Per Cent	No.	Per Cent
30 wk. or less.....	42	28	66.8	15	35.8	6	14.3
31 wk. or more.....	51	29	57.0	6	11.7	1	1.96

TABLE 20.—*Incidence of RLF According to Gestational Age*

		RLF					
		Active		Residual		Blind	
Gestational Age	Infants	No.	Per Cent	No.	Per Cent	No.	Per Cent
25-28 wk.	18	13	72.3	2	11.1	0	0.0
29-30 wk.	24	15	62.5	13	54.1	6	25.0
31-40 wk.	51	29	57.0	5	9.8	1	1.96
Totals.....	93	57	61.3	20	21.4	7	7.5

TABLE 21.—*Neonatal "Anoxia" and RLF*

Birth Weight, Gm.	Infants	RLF		
		Active	Residual	Blind
1000 and less	8	7	1	1
1001-1361	15	10	4	2
1362-1650	8	5	5	2
Totals	31	22	10	5
Per cents	..	70.9	32.2	16.1

C. Anoxia.—Anoxia, along with hyperoxia, has been implicated as an etiologic factor in RLF.[12] Measurements of oxygen saturation were not made in this study. Anoxia was estimated clinically, and this clinical appraisal included a number of features pointing to a poor prognosis: episodes of apnea, grunting respirations, periods of cyanosis in oxygen, inactivity, or other signs of poor aeration and respiratory embarrassment. Among 94 survivors, there were 31 whose neonatal condition was poor and who manifested more than the usual respiratory irregularities of small premature infants during the early neonatal period. The high incidence of RLF in these infants is shown in Table 21.

Eleven of the 15 infants who were most seriously ill neonatally developed active RLF, and 4 were blind (Table 6). Though the numbers are small, they strongly suggest that the risk to an infant with respiratory embarrassment and poor neonatal condition ("anoxia") of developing active RLF and serious visual impairment is greater than for small premature infants in general.

D. Parenteral Fluids.—One item of management possibly linked to RLF is the use of parenteral fluids in the neonatal period. All babies under 1000 gm. received clyses for an average of three weeks. In the next larger group, one-third of the babies received infusions for an average period of two weeks, and in the largest weight group, only 7 of the 40 required clyses for an average of one week. Table 22 presents the data.

TABLE 22.—*Relationship of Clyses and RLF According to Birth Weight and Study Assignment*

Birth Weight, Gm.	Clyses, RLF				No Clyses, RLF			
	Infants	Active	Residual	Blind	Infants	Active	Residual	Blind
Group I								
1000 and less	5	4	1	1	0	0	0	0
1001-1361	10	6	2	1	11	7	4	1
1362-1650	4	2	2	1	18	11	2	0
Subtotal	19	12	5	3	29	18	6	1
Group II′								
1000 and less	1	1	1	0	0	0	0	0
1001-1361	4	2	1	0	16	10	3	1
1362-1650	1	1	0	0	17	7	1	0
Subtotal	6	4	2	0	33	17	4	1
Group II → I								
1000 and less	3	3	1	0	0	0	0	0
1001-1361	2	2	1	0	0	0	0	0
1362-1650	2	2	2	1	0	0	0	0
Subtotal	7	7	4	1	0	0	0	0
Total	32	23	11	5	62	35	10	2
Per cents	..	70.0	35.5	16.1	..	56.0	16.1	3.2

In each weight division, fewer infants in the curtailed oxygen group (II′) received clyses than in the prolonged oxygen groups (I and II → I). One-third of all the babies in the study received clyses, and they had a higher incidence of both active and cicatricial RLF than occurred in the babies who were not given infusions.

A more detailed analysis of these observations with reference to birth weight and neonatal status indicates that these last two features are more directly correlated with the occurrence and severity of RLF than the treatment itself. The smallest and sickest infants received the largest amount of sup-

portive therapy. Thus all the babies under 1000 gm. and all in Group II → I were treated, whereas in the group over 1362 gm., only 7 of 40 infants received clyses.

E. Transfusions.—Transfusions were given, as a rule, to small, weak, and the most immature infants on special indications, most frequently in the latter part of their nursery residence. As in the case of clyses, these criteria resulted in more transfusions for infants at each weight level in Group I than in Group II and to six of seven infants in Group II → I. Approximately one-third of all the babies were transfused, usually around 6-7 weeks of age. Although the incidence of RLF was higher in the transfused than in the non-transfused patients, it seems reasonable to state that the transfusions per se did not cause the disease or influence its course, because babies without transfusions developed RLF, and especially because RLF was detected in almost all cases before transfusions were given, and, with rare exceptions, the disease remained stationary or regressed following transfusions.

Of the 23 babies who received transfusions and had RLF, only one had normal fundi before transfusion. In 15, there were definite eye changes prior to transfusion, and in only 2 of these was there progression of the disease following transfusion. In 11 the active stage of the disease remained unchanged, and in 2 it improved. In seven other babies, transfusion preceded the first funduscopic examination. Two of these showed abnormalities that steadily progressed; in three there was no progression of the changes present at the first examination, and the other two had normal eyegrounds when first seen following three transfusions each. Two weeks after the last transfusion, they both showed evidence of early RLF. Therefore, it seems that the apparent correlation between transfusions as an accessory factor in the causation of RLF is only coincidental.[13]

F. Antibiotics.—The use of antibiotics prophylactically and therapeutically is another new form of treatment given neonatally which might have influenced the occurrence of RLF. In this study it did not play a significant part, for the incidence of RLF was the same among those who received antibiotics as for the study as a whole (Table 23).

G. Intercurrent Illness.—Intercurrent illness had no harmful influence on retrolental disease. After oxygen had been stopped, two babies developed upper and lower respiratory infections due to Staphylococcus aureus. Because of rapid labored respirations with suprasternal and infracostal retractions, they were given antibiotics and placed in Isolette incubators with supersaturated atmospheres and oxygen for 14 and 22 days. Neither showed any evidence of RLF. One infant with cellulitis of the hip and osteomyelitis of the femur had normal eyes; and another baby with S. aureus skin infection and sepsis showed Grade 1 vascular changes which returned to normal. Another infant in poor condition at birth developed sclerema, which cleared. Her eyegrounds showed only Stage 1 changes, which regressed. There were no other serious illnesses.

A search in this study for factors other than oxygen which have been implicated in retrolental disease points to the importance of low birth weight, immaturity (especially

TABLE 23.—*Effect of Antibiotics*

Birth Weight, Gm.	Infants	RLF					
		Active		Residual		Blind	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
1000 and less	7	6	85.5	2	28.6	1	4.6
1001-1361	23	14	60.8	5	21.8	3	13.1
1362-1650	15	8	53.3	4	26.8	1	6.8
Totals	45	28	62.2	11	24.4	5	11.1

those born at a gestational age of 29-30 weeks), and "anoxia" or poor condition at birth as important determinants.

COMMENT

While this study was in progress, reports began to appear which pointed more and more forcefully to the causative role of oxygen in the development of RLF. For example, Crosse,[14] in England, and Gordon,[15] of Denver and Baltimore, began to use in their premature nurseries minimal amounts of oxygen for short periods and then only on specific indications. They found a striking reduction in the incidence of RLF from that observed in previous years. A possible objection to their conclusion that oxygen was the harmful agent is the absence of a contemporary control group. This objection does not hold for two other studies in which the investigators, Patz and his group[16] and Lanman and his co-workers,[17] came to the same conclusion: that excessive concentrations of oxygen for prolonged periods were injurious to the fundi of small premature infants. With the production in animals by Patz and coworkers,[18] Gyllensten and Hellström,[19] Ashton and his collaborators,[20] and by Michaelson[21] of eye changes that resemble human RLF when high concentrations of oxygen were introduced into the environment, the cause-and-effect relationship of oxygen and RLF seemed completely established. The work of Patz ‡ and of Fletcher,[10] depicting the stages of maturation of the fundus, provided the setting in which exposure to oxygen is most likely to be harmful.

The results of the present study were in initial agreement with the above reports. The differences in incidence of the acute disease among the paired infants was at the 5% level of statistical significance by 12 months. As the study progressed, the early advantage shown by Group II was lost, and when this study was terminated so that our nursery could enter a larger cooperative study on the possible role of oxygen in this disease, differences in incidence of active and cicatricial stages of the disease were no longer present between the curtailed and prolonged-oxygen-therapy groups. Such spontaneous fluctuations in incidence of the disease in a hospital nursery have been a frequent source of confusion to previous investigators.

A possible reason for the differences between this study and that of Lanman and coworkers[17] is the inclusion in ours of babies with a birth weight below 1000 gm. in whom the relative incidence of RLF was highest. Furthermore, their infants were followed for only three months, and in our experience a longer period of observation (up to six months) was necessary before final evaluation of residual disease or normal fundi could be made.

Our study differs from Patz's controlled study,[16] in which higher concentrations of oxygen (60%-70%) were used for four to seven weeks in the prolonged oxygen group, and low concentrations below 40% for brief periods up to two weeks were used in the curtailed oxygen group. This plan provided greater contrast between the two groups and might have brought out any differences related to oxygen therapy.

If oxygen administration is important in causing RLF, the similar incidence and course of the disease in Groups I and II of this study may only be explained by the assumption that oxygen exposure for as little as two to seven days with a four-day weaning period, as carried out among Group II infants of 1000-1650 gm., is detrimental. The cooperative study may provide an answer to this question.

Until this possible relationship between oxygen for even short periods and the development of RLF becomes definitely established, it would seem wise to give oxygen at concentrations of 30%-40% only on indication and for the briefest possible period to those infants in real respiratory difficulty, as indicated by cyanosis not improved by suction but relieved by oxygen. That most pre-

‡ Patz, A.: Paper read before the American Academy of Ophthalmology and Otolaryngology, Sept., 1954.

mature infants survive and grow as well on this regimen as on the routine use of oxygen for prolonged periods is shown by Lanman,[17] Gordon,[15] and Crosse and their co-workers and in a separate report from this hospital on this group of infants.[22]

Meanwhile attention should be directed especially to the premature group born at 29-30 weeks of gestation to ascertain if possible the mechanisms for their special susceptibility to RLF. The evidence is sufficiently suggestive even now to encourage obstetricians to make every effort to prolong pregnancy beyond this crucial period. The numbers of babies with potentially serious ocular disturbances might then be considerably reduced.

CONCLUSIONS

In a study conducted on 94 premature infants with birth weights from 800 to 1650 gm., the possible causative role of oxygen therapy in the development of RLF was assessed by a comparison within three weight groups of the effects of curtailed versus prolonged oxygen administration. No significant difference was found with respect to active or cicatricial RLF between babies removed from oxygen at 2, 7, and 14 days with a 4-day weaning-out period and those in oxygen for three to four times as long, nor was there any difference in incidence among the babies at concentrations below 40%, 40%-50%, and above 50%.

The highest incidence of residual changes and blindness occurred in infants with the lowest birth weights, those with a gestational age of 29-30 weeks, and those in precarious condition in the early neonatal period. Other possible factors, such as transfusions, infusions, and antibiotics, that might have influenced the development of RLF in these children were considered, and their relationship to RLF was interpreted as only coincidental.

Although in this study there was not a significant difference in incidence of RLF among the babies in oxygen for curtailed or prolonged periods, oxygen exposure may nevertheless be related to the development of the disease. If so, then the role of oxygen administration as a cause of RLF was masked in this particular study, probably because curtailment of oxygen administration was not drastic enough. It is important to know that RLF does develop with considerable frequency in babies exposed to low or moderate concentrations of oxygen for 5 to 10 days.

Dr. Irwin D. J. Bross did the statistical analysis of the data; Dr. S. Z. Levine gave assistance in this study, and Miss Margaret Zemlock, head nurse of the Premature Nursery, and the pediatric house staff also cooperated in this work.

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Marfan's Syndrome

Report of Five Cases in One Family

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In the year 1896, A. B. Marfan [1] first described the skeletal abnormalities of the syndrome which now goes by his name. Achard,[2] in 1902, called attention to the marked attenuation of the extremities and their excessive length and because of the spiderlike appearance of the hands, called it arachnodactyly. He also was the first to report the familial occurrence of this disease. Salle,[3] in 1912, first noted the association of the ocular and cardiac anomalies (confirmed by autopsy), and he called attention to an increase in the eosinophilic cells in the pituitary. Ormond and Williams [4] focused attention on the frequent association of ectopia lentis and other ocular anomalies with arachnodactyly.

Piper and Irvine-Jones,[5] in 1926, reported the first case in American literature. They stressed the frequency of association of arachnodactyly with congenital malformations of the heart. Weve,[6] in 1931, called attention to the familial incidence of this syndrome; and he speculated that the syndrome was due to a congenital mesodermal defect. Rados,[7] in 1942, in an excellent article, gave a thorough review of the literature and described 10 cases with eye involvement.

Baer, Taussig, and Oppenheimer,[8] in 1943, called attention to the aneurysms of the aorta and medionecrosis cystica of the aorta found in the syndrome and reported two such cases. Etter and Glover,[9] in 1943, reported a death with dissecting aneurysm of the aorta. Parker and Hare,[10] in 1945, reported finding aneurysmal dilatation of the aorta in this syndrome by x-ray examination.

Moehlig,[11] in 1949, reported two cases in which hormonal studies were done with the finding of somewhat elevated 17-ketosteroid excretion in a 6-year-old boy who previously had been treated with methyltestosterone and normal excretion in a 14-year-old boy. He found follicle-stimulating hormone assays to be within normal limits in both patients. He felt that the syndrome results from a primarily inherited pituitary disturbance with a secondary mesodermal tissue defect.

Goyette and Palmer,[12] in 1953, reported the autopsy of a 23-year-old soldier with the syndrome who died from a dissecting aneurysm of the aorta. They added the report of their autopsy to 33 previously reported autopsies, and their summary of the cardiovascular lesions in the syndrome is as follows:

Aortic lesions		22
Dissecting aneurysms	12	
Fusiform aneurysms	7	
Dilated aortic ring	3	
Endocardial lesions		21
Valvular	21	
Mitral	15	
Aortic	10	
Tricuspid	2	
Not specified	2	
Mural	2	
Combined aortic and endocardial lesions		13
Septal defects		9
Patent foramen ovale	7	
Interauricular	1	
Patent ductus arteriosus	1	
Dilated heart (no other data given)		1
Normal heart		1

It is seen that the lesion most commonly found is involvement of the aorta, with 22 out of the 34 reported cases. The aneurysms, even though present during life, may be missed even with careful x-ray studies including barium in the esophagus.

The commonest finding microscopically in the aorta is a rarefication of the media with a total disarrangement of the elastic tissue.

The medial elastica is rarefied and fragmented in some places and lacking entirely in other places. The muscle bundles of the media are also affected and are totally disarranged and separated by cystic spaces. The microscopic lesion strongly resembles Erdheim's medionecrosis cystica, and there is still debate whether the lesions in the two conditions are identical or not.

Hamwi,[13] in 1951, in extensive studies on a man aged 35 years with the syndrome, reported that the serum calcium, inorganic phosphorus, total protein, and alkaline phosphatase were within normal limits. Glucose and insulin tolerance were normal. 17-Ketosteroid excretion was 16 mg. in 24 hours. Metabolic balance studies were done, and he demonstrated the ability of the tissue protoplasm to respond to growth stimuli. He failed to find aberration in the endocrine system. He concluded that total muscle mass, as derived from the creatine coefficient, is normal and that the protoplasmic tissue was capable of responding to growth stimuli by storing nitrogen and phosphorus. He postulated the possibility of some defect in the intermediary metabolism involving the function, transport, or deposition of fat.

There have been electrocardiographic disturbances reported, such as bundle-branch block, partial AV block, auricular fibrillation, and left ventricular strain. These patients frequently die from congestive heart failure, usually from marked aortic insufficiency. Sudden death is common due to dissecting aneurysm. Pneumonia is also a frequent cause of death.

The familial incidence of the disease is well known. Lutman and Neel[14] reported that, in a kinship of 40 persons, 17 members probably had Marfan's syndrome but that there was a great variability in expression of the syndrome in these various members of the family.

The clinical picture of these patients is rather characteristic. They are tall and thin, with long extremities, a dolichocephalic head, prominent long ears, a high forehead, a high-arched palate, and a wizened elderly appearance of the face. They show a marked lack of muscular development and a lack of subcutaneous tissue. Because of that, there is usually a deformity and asymmetry of the chest, dorsal scoliosis, and kyphosis. There may be pigeon breast. The fingers are long, thin, and often webbed. They are double jointed. There frequently is pes planus. Forty to fifty per cent of these patients have eye abnormalities which consist of myopia, bilateral dislocation of the lenses, tremulousness of the iris, small pupils which react poorly to atropine, and shallow anterior chambers. Forty to sixty per cent have cardiac abnormalities, such as septal defects, valvular lesions, and aneurysms of the aorta. These cardiac lesions may simulate rheumatic heart disease, or they may have rheumatic valvular lesions superimposed. Pulmonary anomalies are frequent. Some of the patients do not show the complete syndrome, and a forme fruste may be present.

The exact etiology of the syndrome is unknown. The commonest theory is that of an underlying mesodermal defect, though this does not answer the entire picture. The endocrines may play a role. Pituitary involvement has been reported in some cases.

We wish to report five cases of this syndrome in a mother and four children.

REPORT OF CASES

CASE 1.—Mrs. A. B., aged 31 years, consulted one of us (H. H. B.) because of sudden loss of vision in the right eye. She had trouble with her eyes all her life, was always nearsighted, and wore glasses since age 5 years. Her vision was never better than 20/200 in each eye. She is the mother of five children, three girls and two boys. Her past history revealed measles, chicken pox, and mumps. She has always considered herself generally well. She has no headaches, no dizzy spells, and no digestive upsets. She menstruates regularly, every 29 days for about five days. She graduated from high school and was always near the top of her class. Since age 18 years, she has worn a size 12 shoe. She does her own housework.

When she was 10 months old, her mother died. She has a half-sister and a half-brother who are perfectly normal. Her father died at age 54 years from pneumonia. He was 5 ft. 10 in. (177.8 cm.) tall and normal in appearance. Her aunts and uncles are short and fat. Her husband is tall but is normal and well.

Physical examination revealed a very tall woman. Her height was 6 ft. 4 in. (193 cm.), and she weighed 171 lb. (77.6 kg.). The skull was doliochocephalic. The ears were prominent. The eyes were deeply set; sclerae were blue. Vision in the right eye was light perception. Vision in the left eye, with correction, was 20/200. External structures of the eyes were normal. The pupils were contracted, but reacted sluggishly to direct and indirect

Fig. 1 (Cases 1 and 2).—M. L. B. and mother, Mrs. A. B.

stimulation. External ocular muscles were normal. Both lenses were found to be dislocated upward, with notching in the lower borders of the lenses. No iridodonesis. An attempt was made to dilate the pupil of the right eye with homatropine without success. However, when 2% homatropine and 10% phenylephrine (Neo-Synephrine) were used at 10-minute intervals for five times, the pupils dilated well, and upon funduscopic examination, a retinal detachment was found in the superior temporal

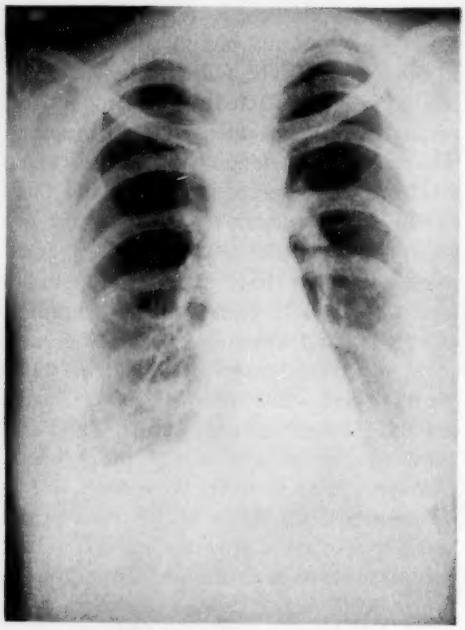
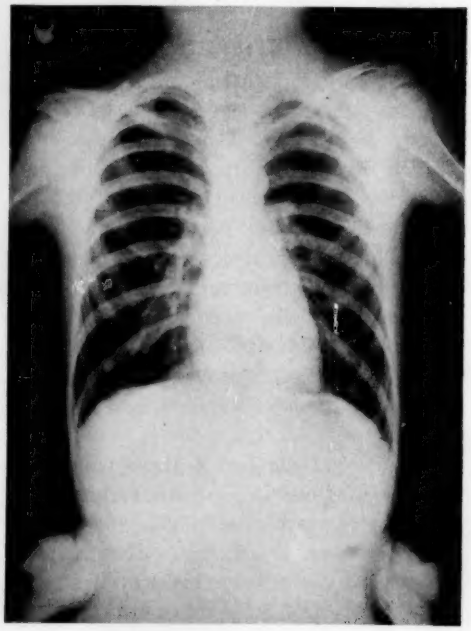


Fig. 2 (Case 1).—Chest x-ray of Mrs. A. B., aged 31 years.

Fig. 3 (Case 2).—Chest x-ray of M. L. B., aged 8 years.



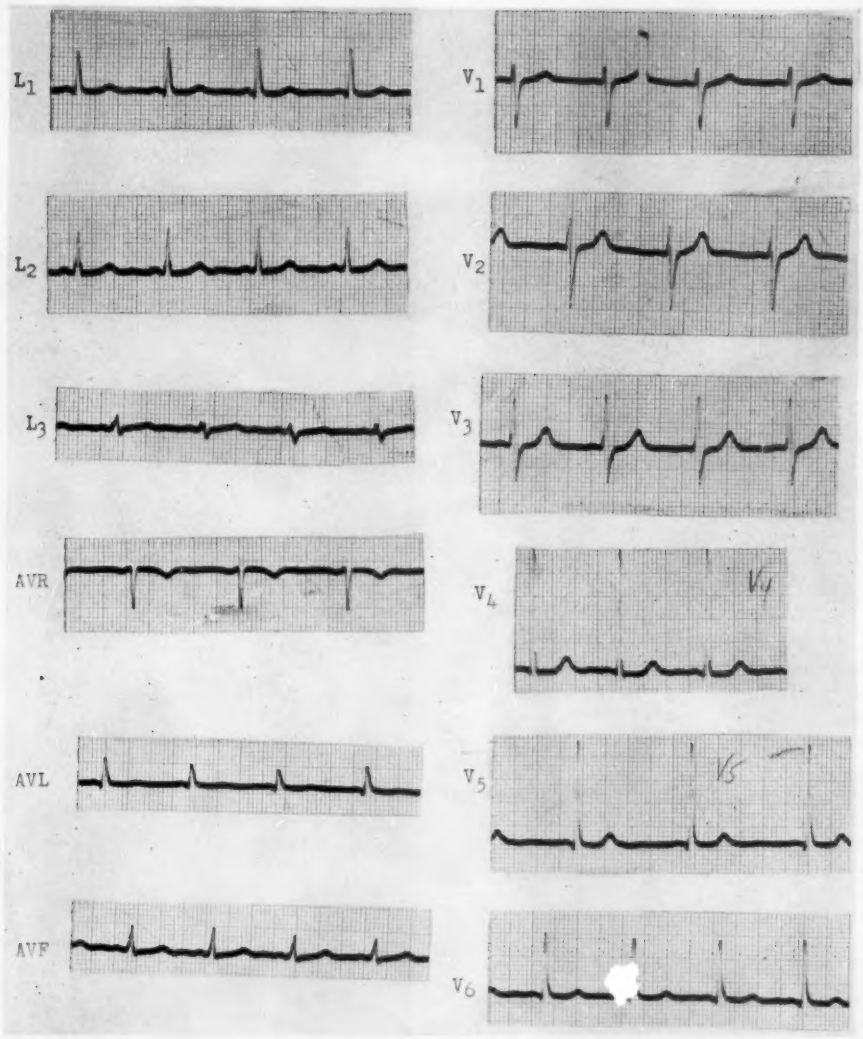


Fig. 4 (Case 1).—Electrocardiogram of Mrs. A. B.

quadrant of the eye. The fundus presented a typical picture of high myopia with conus and myopic changes. The left eye presented the same picture except that there was no retinal detachment. The palate was high and arched. There was marked pigeon-breast deformity of the chest and asymmetry, the right chest being more prominent. Dorsal kyphosis and scoliosis were present. The heart was normal on physical examination. No murmurs were present. Blood pressure was 120/80. Lungs were clear. Liver and spleen were not palpable. Striae gravidarum were present. Extremities were very long and thin, with very long fingers and toes and markedly diminished musculature. There was marked hyperextensibility of the fingers. Her feet showed pes planus, Grade II. Peripheral circulation was normal.

X-ray of the chest revealed the heart to be of normal size and shape. Great vessels were normal. Hila were somewhat prominent. Lungs were clear.

The electrocardiogram revealed regular sinus rhythm, rate 70. Essentially normal electrocardiogram. QRS were of somewhat high amplitude in V_4 and V_5.

Complete blood cell count was normal. Blood sugar and N.P.N. were normal. Urinalysis was normal.

She was admitted to the Montefiore Hospital and operated upon (by Dr. H. Thorpe) for the

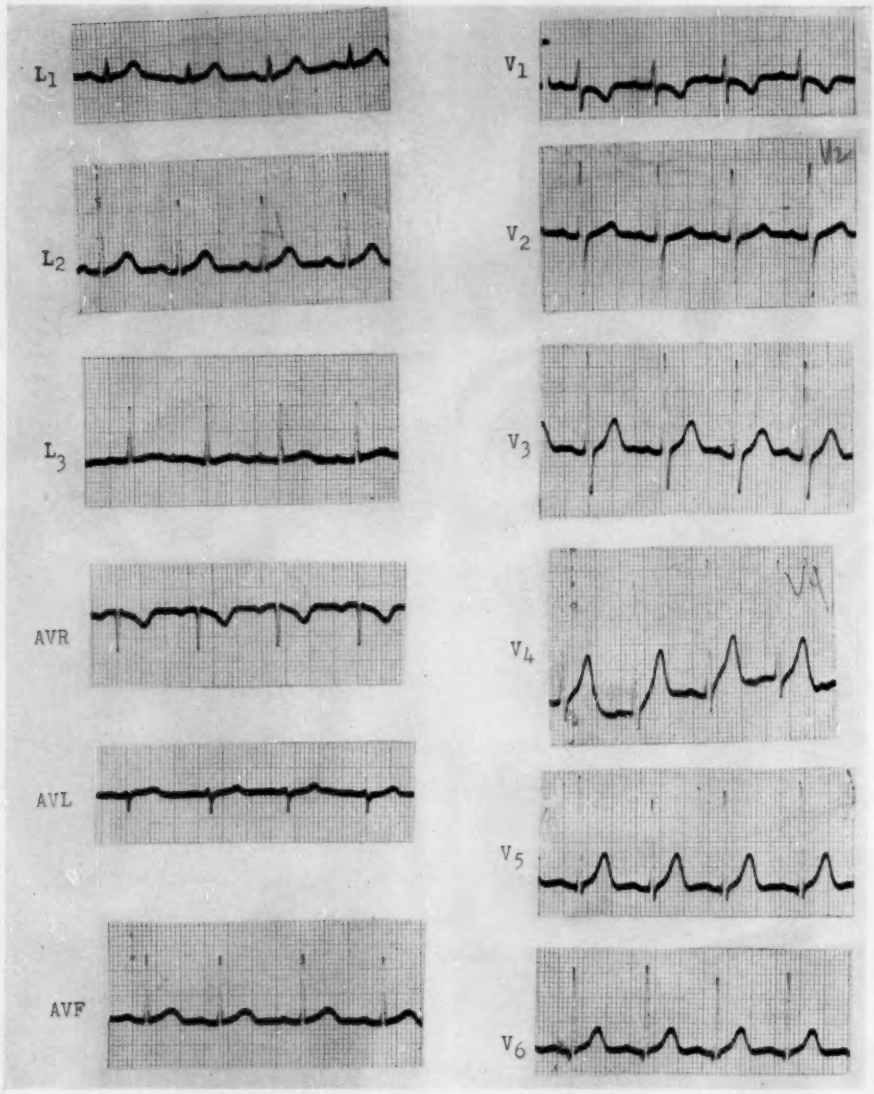


Fig. 5 (Case 2).—Electrocardiogram of M. L. B.

detached retina, with a good result. Her vision in the eye came back to the previous 20/200.

Case 2.—M. L. B., aged 8 years, the daughter of Mrs. A. B., had a normal birth. She had measles, chicken pox, and whooping cough. During the attack of chicken pox, she was suspected of having acute appendicitis and was operated upon. A normal appendix was found, and she subsequently developed intestinal obstruction due to adhesions and was reoperated upon. She has been well since then. She has no headaches. She is in the second grade in school, and she makes good grades. She likes to play and is active; and she has much pep. She wears a size 4½ shoe.

Her height was 4 ft. 7½ in. (141 cm.), and she weighed 55½ lb. (25.1 kg.). She wore glasses. Her eyes showed blue sclerae, dislocated lenses from the nasal side but no notching, and high myopia with myopic conus. Myopia —20 D. The upper teeth were wide-spaced. The palate was high and arched. Her heart was not enlarged on physical examination. A Grade II systolic murmur was present at the apex, transmitted to the left and upward. No thrills were present. A Grade I sys-

tolic murmur was present over the pulmonic area. P_2 was greater than A_2. Lungs were clear. Blood pressure was 110/20. In the abdomen, an operative scar was present in the right rectus. Her fingers and toes were long and showed marked lack of musculature and subcutaneous tissue, and hypermotility was present.

The x-ray of the chest revealed the heart to be of normal size. There was slight fullness in the region of the left auricle. Great vessels were normal. Lungs were normal. Hili were normal.

Fig. 6 (Case 3).—Patient B. J. B., aged 6 years.

Urinalysis was normal.

CASE 3.—B. J. B., a girl aged 6 years, showed very similar development to her 8-year-old sister. She had mumps, measles, chicken pox, and whooping cough. She had a tonsillectomy and adenoidectomy at age 4 years. She is in the first grade at school and is an active youngster.

She was tall and thin, with long extremities with hypermotility of the joints. There was marked asymmetry of the chest, the left side being more prominent than the right. Her eyes were deeply set. The sclerae were blue. Visual acuity was O.D. 15/400, O.S. 15/400. With a —20 sphere, O.D. equaled 20/200 and O.S. equaled 20/200. No iridodonesis. The lenses were dislocated upward. No notching was present. There was high myopia with conus and myopic changes. The palate was high and arched. Teeth were wide-spaced. Her heart was normal in size on physical examination. There was a Grade I systolic murmur of the apex which was not transmitted. Her toes were long and narrow, and hammer toes were present, except in the big toes.

CASE 4.—T. B., a boy aged 3 years, was also tall and thin, with a pigeon breast. He had the long fingers and legs and was double-jointed. There was marked asymmetry of the chest, with the left side being much more prominent than the right. The sclerae were blue. The right eye showed a dislocated lens from below. The left eye was normal. His heart was normal. He had markedly flat feet with eversion with marked hypermotility of the toes.

CASE 5.—D. B., a girl age 15 months, had markedly blue sclerae. There was slight nasal dislocation of the right lens and myopia. She had long fingers and toes. She does not walk yet.

J. B., a boy aged 10 years, was the only member of the family who was entirely normal in appearance and development. He weighed 96 lb. (43.5 kg.) and showed no manifestations of Marfan's syndrome.

COMMENT

In spite of the fact that Marfan's syndrome has been reported in the literature not too infrequently, this condition evidently is still not too well recognized by the general medical profession. It should be brought to their attention if for no other reason than to emphasize the familial characteristics of this syndrome and the advisability of not bringing too many children so afflicted into the world. As this mother put it: "I was never aware that there was anything abnormal about me or my children, except that they were somewhat tall and thin. If I had known, I would not have had five children." Since these cases do develop heart lesions and other complications which frequently terminate their lives early, it is important to be aware of the syndrome and to be able to recognize it.

In this family, the only one who shows a suggestion of a cardiovascular lesion is

M. L. B., aged 8 years, who may have mitral insufficiency. We could not get the other children into the office for more careful cardiologic study; but there is no question about having them having Marfan's syndrome, and they will be observed further from time to time. We wish to call attention to the fact that all these youngsters had blue sclerae, though this may be just a family characteristic. We also wish to emphasize that, out of five children, only one appears entirely normal thus far. We could not follow through the other members of the family on the mother's side to see whether any more cases of Marfan's syndrome might be found in the family.

SUMMARY

We are reporting the cases of a mother and four children with Marfan's syndrome.

The literature is briefly reviewed and the cardiovascular and ocular complications emphasized.

The medical profession should be more aware of this syndrome and be able to recognize it because of the hereditary implications.

500 Penn. Ave.

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The Child with Hemiplegia

A Study of Complications Associated with the Treatment of the Handicapped Arm

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Increasing attention has been directed, in recent years, to the problem of chronic physical disability.[1] Comprehensive programs for the rehabilitation of the cerebral palsied child are now generally established.[2] Because of the relative mild handicap of the hemiplegic child, obvious complicatons in the course of rehabilitation and education of the hemiplegic have been overlooked. The frequent occurrence of mental retardation, speech disorders, seizures, and behavior disturbances in children with hemiplegia is not generally recognized. Phelps [3] has called attention to these complications and the importance of dominance shifts in relation to the hemiplegia. In most rehabilitation centers, the affected arm in the hemiplegic child is treated vigorously without regard to the possible disastrous sequelae of such treatment when it involves the inherited dominant side. This is particularly true in those hemiplegias acquired at birth, during infancy, and in the preschool period. Before any treatment is undertaken for the handicapped arm of the hemiplegic child, it is of extreme importance to determine whether the handicap is on the inherited dominant handedness side or on the subdominant side. Since most investigators believe that "handedness" is an inherited factor, the handedness background of the grandparents, parents, and siblings of each child should be evaluated before treatment is instituted.

From the Cerebral Palsy Clinic and Rehabilitation Center, New Jersey Orthopaedic Hospital, Hospital Center, Orange, N. J., and the Crippled Children Commission, Department of Health, State of New Jersey.

Uncomplicated hemiplegias, then, are those with involvement of the subdominant arm. The "complicated" hemiplegias on the other hand, are those children with handicaps of the inherited dominant side. The inherited dominant side is usually the right. The complicated hemiplegias may exhibit such variations as speech disorders, seizures, mental retardation, and behavior disturbances. These complications develop when a complete shift of dominance or handedness to the subdominant side is required. A complete shift to the subdominant hand takes place in early infancy when the handicap in the arm is so severe from the time of birth that the child does not manipulate the hand at all. These "complete shifts" rarely have such complications with speech, seizures, and mental retardation. If the handicap is mild, then the tendency to shift is delayed because of the strong drive to use the inherited dominant hand despite its handicaps. This results in an incomplete shift of the dominant hand. When a hemiplegic child develops such complications as speech disorders, seizures, mental retardation, or behavior disturbances, an incomplete shift is in progress. Then, every effort must be made to complete the shift to the subdominant hand as quickly as possible. This can be accomplished by avoiding all treatment for the handicapped arm, and concentrating effort on training the uninvolved hand to be as skillful as possible. Occasionally, in order to complete the shift, it may be necessary to immobilize the handicapped arm in a sling or cast.

It is important, then, to adopt entirely new concepts in planning the treatment of children with hemiplegia. The natural tendency is to be vigorous in directing therapy to the handicapped member in order to obtain max-

imum improvement. This treatment may incur disastrous complications, because it may throw back the shift to the handicapped inherited dominant arm, and thus prevent the completion of the shift. One should first try to determine the inherited dominant side from the "handedness" of the parents and siblings of the patient. If this cannot be accomplished with a reasonable degree of certainty, it has been our experience that it is much safer, then, not to treat the handicapped arm at all with occupational therapy or braces until sufficient time has elapsed to observe that the child is free of seizures, without speech or behavior variations, and that he is progressing normally in school. From 1948 through 1953, a study was made of 87 children with hemiplegia from several hundred cerebral palsied children under treatment at the Cerebral Palsy Clinic and Treatment Center of the New Jersey Orthopaedic Hospital. During this five-year period, these hemiplegic children were personally examined and evaluated at intervals of three months and under continuous observation of the staff therapists. Psychological studies were all made by Dr. Harry V. Bice, of the Crippled Children Commission staff. Many of these patients had been previously examined and observed by Dr. Winthrop M. Phelps, in Crippled Children Commission Clinics, prior to 1948, and his careful observations were made available for this study. In addition to the orthopedic and psychological evaluations, the study also included electroencephalograms, audiometry, and consultations with the unit physical therapists, occupational therapists, and speech therapists. The unit social worker and coordinator completed all the detailed history information forms and arranged conferences with the parents of each child wherever practical.

RESULTS (EIGHTY-SEVEN HEMIPLEGIC CHILDREN)

Follow-Up.—The range of follow-up of this group was from 6 months to 168 months (14 years). The average follow-up period was 38.4 months. The great majority of the children were under observation in this clinic for the full five-year period (1948-1953).

Age.—At the time of this report, the average age was 7.9 years. The ages ranged from 9 months to 18 years. At the inception of this study, the large majority of the children were in infancy or in the preschool years.

Sex.—The sex incidence was as follows: male hemiplegic children, 49; female hemiplegic children, 38.

Clinical Classification of Hemiplegia.—The following is the distribution of cases according to clinical classification: spastic, 70; rigidity, 13; athetoid, 4.

Etiology of the Hemiplegia.—The etiology of the hemiplegia was as follows:

Presumptive cause	
Fetal injury, anoxia, and other	72
Posteonvulsive	10
Postencephalitis	1
Postoperative	1
No data available	3

Of the 87 infants, 3 were premature, 81 were born at term, and for 3 no data on the length of the pregnancy were available.

Arm Involved.—In 49 cases the right arm was involved; the left arm was involved in 38.

Dominant Handedness of Parents and Siblings.—The dominant handedness of parents and siblings showed the following distribution:

1. Parents	
Both parents right-handed	75
Both parents left-handed	0
Mixed	8
No data available	4
2. Siblings	
Predominant right	49
Mixed	7
No data available	31

Relationship of Side of Handicap to Inherited Dominant Hand.—The relationship of the side of the handicap to the inherited dominant hand was as follows:

Handicap in inherited dominant hand (shift definitely required)	44
Handicap in inherited subdominant hand (shift not required)	32
Dominant hand undeterminable	9
Insufficient data	2

Incomplete Shift of Dominant Hand.—The data showing the number of incomplete shifts as compared with the number of required shifts are as follows:

	Patients
Shift definitely required	44
Shift may or may not be required	9
Total	53
Number of incomplete shifts	15

COMMENT

The etiological survey produced several interesting facts. Following a pattern noted in studies of the histories of cerebral palsied children in our clinic, there is a greater frequency of a plausible history of birth trauma in the group of hemiplegic children than in the other groups. The greater majority, by far, of these hemiplegics were born out of full-term prgenancies, whereas, in the paraplegic group, prematurity predominantly loomed as an etiological factor.

The hemiplegia on the right side prevailed over left-sided hemiplegia in the ratio of 49:38. It is interesting to note that 75 of the 87 patients studied had parents who were both dominantly right-handed. Since "handedness" is presumed to be inherited, the possibility of the hemiplegic child's being handicapped on the inherited dominant side was very great, indeed. The patients, then, with handicapped left arms were fairly safe from developing the complications of speech disorder, mental retardation, seizures, and behavior variations, since they had the greater possibility of inheriting right-handedness, with no shift of handedness required. Because of this preponderance of right-handedness in parents, 44 of the 87 children were definitely required to shift handedness from the handicapped inherited dominant side to the inherited subdominant arm. Thirty-two children were not required to shift handedness from the handicapped side because their handicap was on the subdominant side according to the dominant handedness of their

TABLE 1.—*Complications of Group*

	Speech Disorders	Mental Retardation	Seizures				Personality or Behavior Problems
			Neonatal Period	After 3 Mo.	Controlled Medication	Uncontrolled	
Shift required, 44 patients	6	9	1	14	2	13	11
Shift not required, 32 patients	1	0	1	9	7	3	1
Shift may or may not be required, 9 patients	2	3	0	3	2	1	1

TABLE 2.—*Complications Associated with Occupational Therapy for Handicapped Arm (Total Forty-One Patients)*

	Speech Disorders	Mental Retardation	Seizures		Personality or Behavior Disturbances
			Controlled	Uncontrolled	
Shift required, 22 patients	4	4	2	2	2
Shift not required, 11 patients	1	0	1	0	0
Shift may or may not be required, 8 patients	0	1	0	1	0

TABLE 3.—*Complications Associated with Bracing for Handicapped Arm (Total Twenty-One Patients)*

	Speech Disorders	Mental Retardation	Seizures		Personality or Behavior Disturbances
			Controlled	Uncontrolled	
Shift required, 14 patients	4	3	2	2	2
Shift not required, 4 patients	1	0	1	0	0
Shift may or may not be required, 3 patients	2	0	0	1	0

parents and siblings. In nine instances, the inherited dominance could not be determined because of the mixed handedness of the parents, that is, one parent dominantly right-handed and the other left-handed.

As noted in Table 1, the highest incidence of the complications of speech disorders, mental retardation, seizures, and behavior disturbances appeared in the group of 44 patients who were required to shift handedness to the subdominant side because of a handicapped inherited dominant arm. The high incidence of seizures in this group is reflected in Table 1. These seizures were first observed in 14 children in this group after the neonatal period, as against one child with seizures noted in the first three months of life. Of the 15 children in this group with seizures, 13 had seizures which could not be adequately controlled by medication during this period of required shift of dominance. This is in sharp contrast to the group who were not required to shift handedness, wherein 7 of the 10 children with seizures were adequately controlled by medication.

As noted in Table 2, 41 children received occupational therapy for the handicapped arm. In the group of 22 patients receiving therapy to the inherited dominant handicapped hand, the incidence of speech disorders and mental retardation was almost 4 to 1 over the group where no shift was required and more than 2 to 1 for those with seizures and personality disturbances. In the group of children wearing a brace on the handicapped member, complications developed with greater incidence in those 14 children who were required to shift handedness to the subdominant side (Table 3).

Of the 15 children classified as "incomplete shift" because of the presence of these complications, 14 had seizures, 11 showed emotional and behavior disturbances, 9 were mentally retarded, and 6 presented speech disorders. A child was classified as an "incomplete shift" when he presented at least two or more of these complications. As soon as these complications were noted and verified, treatment for the handicapped arm, both occupational therapy and bracing, was stopped immediately, and treatment was directed at the uninvolved arm to make it as skillful as possible and thus help to complete the shift. When this was done, invariably the speech improved, seizures stopped or were more amenable to control with medication, personality and behavior improved, and better psychological scores were noted.

It has been our impression that, if one is not absolutely positive that the handicapped arm is on the inherited subdominant side, it is wiser to avoid these disastrous complications by not treating the handicapped arm with occupational therapy and bracing. Although the natural tendency is to treat the handicap vigorously, whether in the arm or in the leg, great caution must be exerted in the handling of the hemiplegic arm. We have observed that in most cases where an incomplete shift develops, the arm is not too severely handicapped. For this reason, the child is not forced to become strongly "one-handed" on the subdominant side, but uses both hands almost equally well, thus delaying the shift to the uninvolved member. It may be necessary, at this point, to immobilize the handicapped arm, when complications denote the development of an incomplete shift. Intensive occupational therapy is then directed to the subdominant uninvolved arm. This will speed up the shift and will avoid the disastrous complications in hemiplegic children of speech disorders, mental retardation, seizures, and behavior disturbances.

SUMMARY

The frequent occurrence of speech disorders, mental retardation, seizures, and behavior disturbances in children with hemiplegia is not generally recognized. These complications appear in hemiplegic children who do not make a complete shift of dominance and handedness from the handicapped inherited dominant side to the uninvolved inherited subdominant arm. A study of 87

children with hemiplegia in a cerebral palsy clinic and treatment center revealed that 44 patients were required to shift handedness from the handicapped inherited dominant side to the uninvolved subdominant hand. Of these 44 children, 15 children were classified as "incomplete shifts" because they developed such complications as speech disorders, seizures, mental retardation, and behavior variations. These disastrous complications can be avoided by withholding occupational therapy and bracing of the handicapped arm, directing therapy only to the uninvolved arm to speed the completion of the shift and occasionally immobilizing the handicapped arm.

31 Lincoln Park.

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2. Keats, S.: Cerebral Palsy: Selection and Training of the Child with Normal Mentality, Am. J. Dis. Child. **79**:124 (Jan.) 1950.

3. Phelps, W. M.: Dominance Shifts in Relation to Hemiplegia, Proc. Spring Conference of Child Research Clinic of the Woods Schools, Langhorne, Pa., May 17, 1946.

News and Comment

ANNOUNCEMENTS

Courses in Pediatric Hematology.—University of Pennsylvania, The Graduate School of Medicine, announces two short courses in pediatric hematology for practitioners, to be given at the Children's Hospital of Philadelphia, in conjunction with the centennial celebration of the hospital, June 6-8 and 9-11, 1955.

I. *Practical Pediatric Hematology.*—Monday, Tuesday, and Wednesday, June 6, 7, and 8, from 9:30 a. m. to 4:30 p. m.

This course will be under the direction of Dr. Irving J. Wolman, Associate Professor of Pediatrics and Hematologist to The Children's Hospital of Philadelphia. Dr. Wolman will be assisted by Dr. Benjamin Dickstein, Dr. Paul G. Eglick, Dr. George W. Ward, Dr. Harold A. Wurzel, Dr. Timothy Talbot, and others.

The topics to be covered in this three-day course will include normal ranges for hemoglobin, erythrocytes, leucocytes, and platelets, as related to age, prematurity, etc.; performance and interpretation of the bone marrow examination; the various childhood anemias and approaches to their investigation; splenomegaly and related disturbances; the hemorrhagic diseases, including the newly recognized subvarieties of hemophilia; disorders of the leucocytes; diagnosis and management of leukemia; advances in blood grouping and in transfusion therapy.

These subjects will be presented from the standpoints of normal and abnormal physiology, with emphasis on the newer clinical and laboratory approaches. There will be case presentations, conferences, and demonstrations of tests within the scope of the office laboratory.

Each registrant will be given a collection of representative blood and bone marrow smears.

II. *Rh and Other Blood-Group Incompatibilities in Relation to Erythroblastosis Fetalis.*—Thursday, Friday, and Saturday, June 9, 10, and 11, from 9:30 a. m. to 4:30 p. m.

This will be under the direction of Dr. Neva M. Abelson, Assistant Professor of Pediatrics and Director of the Philadelphia Serum Exchange of The Children's Hospital. Dr. Abelson will be assisted by Dr. Thomas Boggs.

The topics to be covered in this three-day course will include serology of Rh and other blood groups; exchange transfusion; practical demonstrations of serologic procedures and exchange transfusion.

Tuition for each course: $60.00, payable with the completed application.

Address requests for application forms or other information to The Dean, Graduate School of Medicine, 230 Medical Laboratories, University of Pennsylvania, Philadelphia 4.

Cortisone Therapy of Initial Attacks of Rheumatic Carditis

I. Clinical Data

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INTRODUCTION

The role of cortisone in prevention of residual cardiac damage following initial attacks of rheumatic heart disease is still not clear despite many reports of its administration.* The majority of the reports suggest that it was probably without value though the types of cases, their chronicity and severity, and the duration of cortisone dosage and its magnitude as well as associated therapy varied. At least several workers feel that this agent in conjunction with an adequate regimen is efficacious in controlling and preventing residual cardiac damage.† Our findings are in keeping with those of the latter group. This paper presents our experience with 53 children treated with large doses of cortisone in their initial attack of clinically unequivocal rheumatic carditis. The results suggest that cortisone in large amounts under the regimen employed may prevent cardiac abnormalities in patients without previous heart damage when given within six weeks of onset of rheumatic fever.

From Department of Research Medicine and Children's Hospital of University of Pittsburgh School of Medicine.

Aided by grants from United States Public Health Service, Kiwanis Club of Pittsburgh, and National Drug Company, Philadelphia.

* References 1-46.

† References 3-6, 20, 24-27, 31, 36, 37, 45, and 46.

PATIENTS AND METHOD OF STUDY

Only children with unequivocal clinical evidence of cardiac involvement prior to therapy were included in this study. Their ages ranged from 3.9 to 15.4 years. Two of these patients were subsequently re-treated after 19 and 27 months when recurrent attacks occurred. The second attacks are included in the analysis, bringing the total number to 55, since the children had been followed carefully enough to be certain they had no cardiac abnormalities.

The diagnosis was established by criteria more strict than those of Jones,[47] since we have not included any patients in whom there might be doubt of clinically recognizable carditis. In keeping with this, an additional five patients were treated with cortisone but were omitted from this report, since they did not have endocarditis, despite electrocardiographic changes, tachycardia, and other full-blown findings of rheumatic fever. They do not have residual cardiac abnormalities. The criteria of Jones are listed for ease of reference.[47]

CRITERIA FOR DIAGNOSIS

Minor.—1. Beta hemolytic streptococcal infection enlargement, congestive failure, pericarditis, apical or aortic diastolic murmurs, and a Grade 2 or louder systolic murmur at the apex transmitted to the left axilla (grading scale: 1 to 4). Faint apical systolic murmurs not transmitted to the left axilla were graded 1 and not considered evidence of endocarditis. 2. Polyarthritis. 3. Subcutaneous nodules. 4. Erythema multiforme or marginatum. 5. Chorea.

Minor.—1. Beta hemolytic streptococcal infection within one month preceding onset of illness. 2. Fever. 3. Epistaxis. 4. Abdominal pain. 5. Prolonged P-R interval in electrocardiogram (Ashman-Hull tables).[48] 6. Increased sedimentation rate, anemia, leucocytosis. 7. Abnormal serum proteins. 8. Previous history of rheumatic fever.

Duration of illness was judged from first major manifestation or any minor one which seemed directly related to the symptoms of rheumatic fever.

The patients were evaluated by history, complete physical examination, and laboratory studies,[49] including nose and throat cultures; complete blood cell counts; urinalyses; antistreptolysin O titers [50]; blood nonprotein nitrogen, sugar, and eosinophile counts; serum total carbon dioxide content, chloride, sodium, potassium, total protein, albumin, globulins, cholesterol, phosphorus; electrocardiogram; chest x-ray (teleoroentgenogram) with barium swallow, and frequent fluoroscopy. The majority of these determinations were repeated at weekly intervals. Laboratory data are presented in another paper.[51]

X-rays and fluoroscopic examinations were repeated once a month while patients were hospitalized, more often only if indicated. Cardiac enlargement was evaluated by cardiothoracic ratios,[52] esophagram, shape of heart, physical examination, and fluoroscopy. In addition, daily weights and blood pressures were recorded, the latter one or more times each day. In a few instances height was measured. Rectal temperatures, pulse, and respiratory rates (nonsleeping) were determined four times a day. On admission all patients had both negative tuberculin skin tests and negative serological tests for syphilis.

THERAPEUTIC REGIMEN

The therapeutic regimen was as follows: 1. Bed rest was carried out. 2. Cortisone was given in varying amounts and routes throughout the study but in the majority of patients, as oral medication, 100 mg. every eight hours for six weeks and then gradual tapering until cessation after two more weeks; the medication was withdrawn according to the following schedule: 100 mg. every 12 hours for two days; 75 mg. every 12 hours for two days; 50 mg. every 12 hours for two days; 37.5 mg. every 12 hours for two days; 25 mg. every 12 hours for two days; 12.5 mg. every 12 hours for the last four days. Five patients received corticotropin (ACTH) during the final week of therapy. If the disease still seemed active at the end of this interval, the patient was retreated. 3. Diets were rigidly limited in sodium to 2.5 to 10 mEq. per day and contained 150 mEq. of potassium and adequate protein and Calories, plus supplementary iron and vitamins. When therapy was discontinued, the diet became general. 4. Penicillin was given, 400,000 or 800,000 units intramuscularly or 500,000 units orally, twice a day for the first week; treatment was then continued both inside and outside the hospital with oral buffered penicillin, 100,000 units three times a day between meals. During the last week of therapy with cortisone, several patients also received oxytetracycline (Terramycin), 250 mg. four times a day, and larger amounts of penicillin. 5. Digitalis and, in some patients, mercurial diuretics were given if congestive heart failure was present.

FOLLOW-UP

The patients were followed in a special clinic after discharge from the hospital. They were usually seen in two weeks, then at monthly intervals for the next three months, and finally every third month for the following year. Thereafter they returned to clinic at three- to six-month periods. More frequent visits were arranged when necessary. Penicillin as described above was continuously administered. If sensitivity to penicillin occurred, sulfadiazine, 0.5 gm. twice a day, or erythromycin, 200 mg. twice a day, was given.

RESULTS

Tables 1, 2, and 3 describe the clinical and cardiac findings prior to, during, and after the cortisone therapy as indicated. The patients are divided into three categories to evaluate the importance of duration of illness prior to cortisone treatment. Table 4 describes the regimen of cortisone and Table 5 summarizes the duration of illness and number of patients in each group, as well as sex of the patients. Tables 6 through 8 summarize the clinical and cardiac data prior to and after treatment.

I. CLINICAL

A. Clinical Findings Prior to Therapy.—Fever was most commonly present; the few patients without it had received acetylsalicylic acid prior to hospitalization. Polyarthritis and arthralgia were next in order of frequency, followed by sore throat. The family history was positive for rheumatic fever in 31% of the patients. One-quarter of the children had nosebleeds; 20% had rashes, and another 20%, abdominal pain. Ten per cent of the patients had subcutaneous nodules (Table 6).

The striking differences among the three groups were the higher percentages of subcutaneous nodules and of the skin rashes in the group ill more than six weeks.

B. Cardiovascular Findings Prior to Treatment.—More than half of the patients had cardiac enlargement (Tables 1-3), based upon the cardiac mensuration by teleoroentgenogram. Eighty per cent of this group had congestive failure, and all of these patients had cardiac enlargement.[53] Pericarditis

TABLE 1.—*Clinical Findings in Patients Treated Within Two Weeks of Onset of Rheumatic Carditis*

				Noncardiac Findings Prior to Treatment										Cardiac Findings Prior to Treatment					Treatment		Status at End of Treatment				Follow-Up	
Patient	Age, Yr.-Mo.	Sex	Race	Days of Illness Before Treatment	Sore Throat	Fever	Nosebleed	Abdominal Pain	Erythema Multiforme or Marginatum	Polyarthritis	Arthralgia	Subcutaneous Nodules	Positive Family History	Enlarged Heart	Congestive Failure	Pericarditis	Murmurs*	Tachycardia	Prolonged P-R	Duration, Days	Cortisone, Gm.	Cardiac*	Reactivation	Fever	Sed. Rate Increase	Duration, Mo.	Cardiac Status*
S. M.	5-4	M	W	9	+	+	+	+	0	+	—	0	0	++	+	0	MI	+	+	10	3.0	MI[1]	0	0	0	32	Norm.
L. B.	3-11	M	W	14	+	+	0	0	0	+	—	0	0	++	+	0	MI	+	+	42†	16.1	EH, MI	0	+	+	34	EH, MI
E. B.	11-0	F	W	14	+	+	0	0	+	+	—	0	+	0	0	0	MI	+	+	42	12.6	Norm.	0	+	+	23	Norm.
J. L.	12-4	M	W	10	0	+	0	0	0	+	—	0	+	0	0	0	MI	+	+	40‡	7.5	MI[1]	0	0	+	29	Norm.
C. T.	6-0	M	W	14	+	+	0	+	0	+	—	0	0	0	0	0	MI	+	+	50	8.7	Norm.	0	0	0	18	Norm.
D. C.	7-0	M	W	14	+	+	0	0	0	0	0	0	0	0	0	0	MI	+	0	51	10.2	Norm.	0	0	0	17	Norm.
F. F.	9-11	M	W	14	+	+	0	0	0	0	+	0	0	0	0	0	MI, AI	+	+	56	10.2	Norm.	0	0	0	18	Norm.
L. M.	13-3	F	W	10	+	+	0	0	0	+	—	0	0	+	+	0	MI	+	+	56	14.6	Norm.	0	0	0	12	Norm.
H. P.	8-10	F	W	4	+	+	0	0	0	+	—	0	0	+	+	0	MI	+	0	56	14.6	Norm.	0	+	0	12	Norm.
T. K.	7-0	M	W	7	0	+	+	+	0	+	—	0	+	0	0	+	MI, AS	+	0	56§	13.8	Norm.	0	+	+	8	Norm.
H. R.	14-7	F	W	12	+	+	0	0	0	+	—	0	0	0	0	0	AI	+	0	56	13.8	AI	0	0	0	5	AI, MS
C. K.	8-10	F	W	13	0	+	0	+	0	+	—	0	0	0	0	0	MI	+	0	56	13.8	Norm.	0	0	0	14	Norm.
G. G.	6-7	M	W	10	+	+	0	0	0	+	—	0	0	0	0	0	MI	+	0	56	13.8	MI[1]	0	+	0	6	Norm.
P. Z.	7-6	M	W	7	0	+	0	+	0	+	—	0	0	0	0	0	MI	+	0	84	19.2	Norm.	0	+	+	16	Norm.

* MI indicates mitral insufficiency; MI[1], a Grade 1 (total grading 1-4) apical systolic murmur not transmitted; EH, enlarged heart; AI, aortic insufficiency; AS, apical systolic; MS, mitral systolic.

† Received cortisone for first 35 days, total amount 16.1 gm., and corticotropin (ACTH) for 7 more days at end, total amount 0.46 gm.

‡ Received 100 mg. corticotropin q. d. for 10 days then the cortisone.

§ Last 5 days received corticotropin, 100 mg. per day, together with cortisone.

TABLE 2.—*Clinical Findings in Patients Treated Two to Six Weeks After Onset of Rheumatic Carditis*

				Noncardiac Findings Prior to Treatment										Cardiac Findings Prior to Treatment						Treatment		Status at End of Treatment				Follow-Up	
Patient	Age, Yr.-Mo.	Sex	Race	Days of Illness Before Treatment	Sore Throat	Fever	Nosebleed	Abdominal Pain	Erythema Multiforme or Marginatum	Polyarthritis	Arthralgia	Subcutaneous Nodules	Positive Family History	Enlarged Heart	Congestive Failure	Pericarditis	Murmurs*	Tachycardia	Prolonged P-R	Duration, Days	Cortisone, Gm.	Cardiac*	Reactivation	Fever	Sed. Rate Increase	Duration, Mo.	Cardiac Status*
E. W.	12-5	F	W	39	+	+	+	+	0	+	—	0	0	+	+	+	MI	+	+	11	1.1	EH, MI	+	+	+	9	MI
H. J.	11-10	F	W	42	+	+	+	0	0	+	—	0	0	0	0	0	MI	+	0	20	1.6	MI	0	0	0	12	MI
S. B.	6-10	F	W	19	+	+	0	+	+	+	—	0	+	0	0	0	MI	+	0	40	4.0	Norm.	0	0	0	39	Norm.
A. P.	9-3	M	W	54	+	+	0	0	0	+	—	0	0	0	0	0	MI	+	0	42	4.2	Norm.	0	0	0	28	Norm.
C. H.	6-10	F	W	32	+	+	0	+	0	+	—	0	0	+	+	0	MI	+	0	47	14.1	EH, MI	0	+	+	26	MI
H. P.	14-11	M	N	22	†	+	+	0	0	+	—	0	+	0	0	0	MI, AI	+	0	53	14.2	AI	0	0	+	18	Norm.
T. W.	7-6	M	W	41	+	+	+	0	0	0	+	0	0	+	+	0	MI, MD	+	0	61	16.0	Norm.	0	+	0	10	Norm.
H. B.	9-10	F	W	26	+	+	0	0	0	+	—	0	0	0	0	0	MI	+	+	54	14.5	Norm.	0	0	+	14	Norm.
T. H.	7-9	M	W	40	+	+	0	0	0	0	+	0	+	±	0	0	AI, MI, MD	+	+	56	13.8	Norm.	0	+	0	3	MI[1]
V. H.	5-7	F	N	21	+	+	0	0	0	+	—	0	+	+	0	0	MI	+	0	56	13.8	Norm.	0	+	+	4	Norm.
J. S.	9-6	F	W	30	+	+	+	0	0	+	—	0	0	+	+	+	MI	+	0	56	13.8	MI	0	0	+	8	MI
G. S.	10-2	M	W	30	+	0	0	0	0	+	—	0	0	0	0	0	MI	+	0	56	13.8	Norm.	0	0	0	8	Norm.
D. V.	11-3	M	W	42	0	+	0	0	0	+	—	0	+	0	0	0	MI	0	0	56	13.8	MI[1]	0	+	0	6	MI[1]
S. K.‡	5-3	M	W	35	0	+	+	0	0	+	—	0	+	+	+	0	MI, MD	+	0	56	13.8	MI	0	+	0	4	MI
G. B.§	7-3	M	W	28	+	+	0	0	+	+	—	+	0	+	+	+	AI	+	0	56	13.8	Norm.	0	0	0	6	Norm.
R. C.†	11-2	M	W	28	+	+	0	0	0	+	—	0	0	0	0	0	MI	+	0	56	13.8	Norm.	0	+	0	4	MI[1]
R. D.‖	12-5	M	W	30	†	+	0	+	0	+	—	0	0	+	+	0	MI	+	+	56	13.8	MI	0	+	+	5	MI
T. W.§	9-1	M	W	40	+	+	+	0	+	0	+	0	0	+	0	0	MI	+	+	56	13.8	Norm.	0	0	0	1	Norm.
W. B.	3-11	M	W	20	0	+	0	0	+	0	0	0	0	±	+	0	MI	+	0	60	16.4	MI	0	+	+	15	Norm.
C. P.	4-5	M	N	37	+	+	+	+	0	+	—	0	0	+	+	0	MI, MD	+	0	64	17.5	EH, MI	0	+	+	18	EH, MI, MS
M.R.¶	13-0	F	W	17	0	+	+	0	0	+	—	0	+	+	+	+	MI	+	+	65	7.9	MI	0	0	+	35	Norm.
R. T.	8-1	M	W	22	+	+	0	0	0	+	—	0	0	0	0	0	MI	+	+	66	17.2	Norm.	0	+	0	18	Norm.
E. W.	8-3	M	W	20	†	+	0	0	0	+	—	0	+	0	0	0	MI	+	0	70	15.8	Norm.	0	+	+	16	Norm.
E. S.	12-3	F	W	22	+	0	0	0	0	+	—	0	+	0	0	0	MI	+	+	69	13.9	Norm.	0	0	+	17	Norm.
J. T.	8-0	F	W	21	0	+	0	0	0	0	0	0	0	0	0	0	MI	+	0	68	12.0	Norm.	0	+	0	17	Norm.
N. I.	9-2	F	W	30	+	+	+	0	0	+	—	0	0	0	0	0	MI	+	+	86	20.1	Norm.	0	+	0	11	Norm.
F. G.	12-6	F	W	22	+	+	0	0	0	0	0	0	+	+	+	0	MI, MD	+	+	113	24.1	EH, MI, MS	0	0	0	13	EH, MI, MS

* MI indicates mitral insufficiency; EH, enlarged heart; AI, aortic insufficiency; MD, mitral diastolic; MI[1], a Grade 1 (total grading, 1-4) apical systolic murmur not transmitted; MS, mitral systolic.

† Upper respiratory infections.

‡ May have been ill for 6 months, since spontaneous nosebleeds were observed then.

§ Treated in a 2d attack 27 and 19 months, respectively, after their first attack.

‖ History of chorea.

¶ Received corticotropin (ACTH) and cortisone simultaneously; 65 days of corticotropin, 5.32 gm., and 31 days of cortisone, 7.9 gm.

TABLE 3.—*Clinical Findings in Patients Treated Six or More Weeks After Onset of Rheumatic Carditis*

				Noncardiac Findings Prior to Treatment										Cardiac Findings Prior to Treatment						Treatment		Status at End of Treatment				Follow-Up	
Patient	Age, Yr.-Mo.	Sex	Race	Days of Illness Before Treatment	Sore Throat	Fever	Nosebleed	Abdominal Pain	Erythema Multiforme or Marginatum	Polyarthritis	Arthralgia	Subcutaneous Nodules	Positive Family History	Enlarged Heart	Congestive Failure	Pericarditis	Murmurs*	Tachycardia	Prolonged P-R	Duration, Days	Cortisone, Gm.	Cardiac*	Reactivation	Fever	Sed. Rate Increase	Duration, Mo.	Cardiac Status*
M. S.	11-8	F	W	90	+	+	0	0	0	0	0	0	0	+	+	+	MI	+	+	3	0.3	Died	..	..	..	..	....
R. C.	13-2	M	W	240	+	+	0	0	0	+	—	0	0	+	+	+	MI, MS	+	+	5	1.9	Died	..	..	..	..	....
P. M.†	15-5	F	W	135	+	+	0	0	0	+	—	0	0	+	+	+	MI, MD	+	+	10	1.0	EH, MI, MD	+	0‡	+‡	34	MI
G. B.	5-0	M	W	63	+	+	0	0	+	+	—	+	0	+	0	0	MI, AI	+	+	21§	6.5	Norm.	0	+	+	26	Norm.
D. S.†	3-11	M	W	180	+	+	0	0	0	0	—	0	0	+	+	0	MI, MD	+	+	43	10.6	EH, MI	+	0‡	0‡	28	EH, MI
L. P.	8-8	F	W	187	+	0	0	0	+	+	—	+	+	0	0	0	MI	0	0	44	9.6	MI	0	+	0	29	MI
J. A.	13-9	M	W	70	+	+	+	0	+	0	+	+	+	±	0	0	MI	+	0	56	13.8	MI	0	+	+	11	MI
K. M.	10-1	M	W	90	+	+	0	0	0	+	—	0	0	±	+	0	MI, MD	+	0	56	13.8	MI	0	+	0	3	MI
H. E.¶	10-10	F	W	56	0	+	0	0	0	0	0	0	0	+	+	0	MI, MD	+	+	71	18.0	EH, MI	0	+	+	6	EH, MI
L. C.	9-8	M	W	71	‡	+	0	0	+	+	—	+	0	+	0	0	MI	+	0	76	17.4	MI	0	0	0	12	MI
C. S.**	11-1	F	W	56	+	+	0	0	0	+	—	0	+	+	+	0	MI	+	+	83	18.9	EH, MI	+	+‡	+‡	11	MI
J. W.††	6-10	F	W	160	0	+	+	0	0	0	0	0	0	+	+	+	MI	+	+	104	21.4	EH, MI	0	+	0	14	EH, MI
G. L.	9-1	F	N	56	0	+	+	0	0	+	—	0	+	0	0	0	MI, AI, MD	+	0	109	22.3	±EH, MI, AI	0	0	+	23	EH, MI, AI
J. D.	9-2	M	W	53	+	+	0	0	+	+	—	0	0	+	+	0	MI, MD	+	0	107	23.4	EH, MI, MD	0	+	0	17	MI

* MI indicates mitral insufficiency; MS, mitral systolic; MD, mitral diastolic; EH, enlarged heart; AI, aortic insufficiency.

† Retreated with 7.8 gm. cortisone for 37 days.

‡ Fever and sed. rate changes listed in patients who reactivated indicate findings at end of 2d course, since they were both increased at end of 1st.

§ Received corticotropin (ACTH) last 6 days.

¶ Chorea.

‡ Upper respiratory infection.

** Retreated with 7.9 gm. cortisone for 49 days.

†† New attack of rheumatic fever with carditis and heart failure at 17-month follow-up. She had interrupted prophylactic penicillin.

TABLE 4.—*Admission Body Weight and Dose of Cortisone*

Patient	Age, Yr.-Mo.	Sex	Body Weight on Admission, Kg.	Total Cortisone			Maximum Cortisone		
				Gm.	Days	Mg/Kg.	Mg/Day	Days	Mg/Kg/Day
Group 1: Patients Treated Within 2 Weeks of Onset									
S. M.	5-4	M	16.5	3.0	10	181.8	300	10	18.1
L. B.	3-11	M	15.5*	16.5	42	1064.5	493	29	31.8
E. B.	11-0	F	42.3	12.6	42	297.8	300	42	7.1
J. L.	12-4	M	36.9	7.5	40	203.3	200	14	5.3
C. T.	6-0	M	27.2*	8.7	50	319.9	300	14	11.0
D. C.	7-0	M	21.8	10.2	51	467.9	300	28	13.3
F. F.	9-11	M	37.8	10.2	56	269.8	300	22	8.0
L. M.	13-3	F	44.1	14.6	56	331.1	300	42	6.8
H. P.	8-10	F	27.3	14.6	56	534.8	300	42	11.0
T. K.	7-0	M	22.8	13.8	56	605.3	300	42	13.1
H. R.	14-7	F	55.5	13.8	56	248.6	300	42	5.4
C. K.	8-10	F	30.5	13.8	56	452.4	300	43	9.8
G. G.	6-7	M	21.7	13.8	56	635.9	300	41	13.3
P. Z.	7-6	M	21.4*	19.2	84	897.2	300	50	14.0
Group 2: Patients Treated Between 2 and 6 Weeks After Onset									
E. W.	12-5	F	35.0*	1.1	11	31.4	100	11	2.8
H. J.	11-10	F	41.5	1.6	20	38.3	200	1	4.8
S. B.	6-10	F	27.8	4.0	40	108.0	100	40	3.6
A. P.	9-3	M	30.5	4.2	42	137.7	300	4	9.8
C. H.	6-10	F	22.0	14.1	47	640.9	300	45	13.6
H. P.	14-11	M	46.0	14.2	53	308.7	300	48	6.5
T. W.	7-6	M	22.6	16.0	61	707.9	300	47	13.2
H. B.	9-10	F	39.9	14.5	54	363.4	300	46	7.5
T. H.	7-9	M	19.9	13.8	56	693.4	300	42	15.0
V. H.	5-7	F	17.3	13.8	56	797.7	300	43	17.3
J. S.	9-6	M	24.8	13.8	56	556.4	300	43	12.1
D. V.	11-3	M	30.7	13.8	56	449.5	300	45	9.7
S. K.	5-3	M	13.2	13.8	56	1045.4	300	47	22.7
G. B.†	7-3	M	22.9	13.8	56	602.6	300	42	13.1
R. C.	11-2	M	29.1	13.8	56	474.2	300	42	10.3
R. D.	12-5	M	38.9	13.8	56	354.6	300	42	7.7
T. W.†	9-1	M	32.5	13.8	56	424.0	300	41	9.2
W. B.	3-11	M	13.0	16.4	60	1261.5	300	51	23.1
C. P.	4-5	M	15.5	17.5	64	1129.0	300	57	19.3
M. R.	13-0	F	38.6	7.9	65	204.6	300	24	7.7
R. T.	8-1	M	28.7	17.2	66	599.3	300	52	10.4
E. W.	8-3	M	44.1	15.8	70	358.3	300	44	6.8
E. S.	12-3	F	37.0	13.9	69	375.6	300	37	8.1
J. T.	8-0	F	24.6	12.0	68	487.8	300	28	12.2
N. I.	9-2	F	24.6	20.1	86	817.0	300	58	12.2
F. G.	12-6	F	23.4	24.1	113	1029.0	300	68	12.8
Re-treatment									
E. W.	.....	F	39.5	1.0	10	25.3	100	10	-2.5
Group 3: Patients Treated 6 or More Weeks After Onset									
M. S.	11-8	F	31.9	0.3	3	9.4	100	2	3.1
R. C.	13-2	M	....	1.9	5	.....	800	2	....
P. M.	15-5	F	46.9	1.0	10	21.3	100	10	2.1
G. B.	5-0	M	14.5	6.5	21	448	500	10	34.5
D. S.	3-11	M	15.0	10.6	43	706	300	27	20.0
L. P.	8-8	F	24.6	9.6	44	390	300	26	12.2
J. A.	13-9	M	31.3	13.8	56	440	300	42	9.6
K. M.	10-1	M	29.1	13.8	56	474	300	43	10.3
H. E.	10-10	F	30.2	18.0	71	586	300	55	9.8
L. C.	9-8	M	26.5	17.4	76	656	300	42	11.3
C. S.	11-1	F	40.3	18.9	83	468	300	58	7.4
J. W.	6-10	F	20.8	21.4	104	1028	300	53	14.4
G. L.	9-1	F	30.9	22.3	109	721	300	46	9.7
J. D.	9-2	M	25.9	23.4	107	903	300	52	11.6
Re-treatment									
P. M.	.....	F	47.5	7.8	37	164	500	10	10.5
C. S.	.....	F	48.3	7.9	49	163	300	14	6.2
D. S.	.....	M	14.9	7.8	37	523	300	15	20.1

* Weights obtained shortly after admission.

† Second admission with active rheumatic carditis.

TABLE 5.—*Age, Sex, and Race of Patients with Rheumatic Carditis*

Duration of Illness, Wk.	Total No. Patients	Age, Yr.		Sex, Male	Race, White
		Mean	Range		
<2	14	8.7	3 11/12-14 7/12	9	14
2-6	27	9.2	3 11/12-14 7/12	15	24
>6	14	9.9	3 11/12-15 5/12	7	13
Total	55			31	51

TABLE 6.—*Clinical Findings Before Cortisone Treatment of Initial Attack of Rheumatic Carditis*

Onset, Wk.	Total No. Patients	Poly-arthritis	Nodules	Rash	Fever	Sore Throat	Epi-staxis	Abd. Pain	Family History	Arth-ralgia
<2	14	12	0	1	14	10	2	5	3	1
2-6	27	21	1	4	25	22	10	5	10	3
>6	14	9	4	5	13	11	3	0	4	1
Total	55	42	5	10	52	43	15	10	17	5

TABLE 7.—*Cardiac Findings Before Cortisone Treatment of Initial Attack of Rheumatic Carditis*

Onset, Wk.	Total No. Patients	Cardiac Enlarg.	Congest. Failure	Peri-carditis	Murmurs*						ECG P-R Abn.
					MI	MI, MD	MI, AI	MI, AS	AI	MI, MD, AI	
<2	14	4	4	1	11	0	1	1	1	0	7
2-6	27	14	11	4	20	4	1	0	1	1	10
>6	14	12	9	4	6	6	1	0	0	1	8
Total	55	30	24	9	37	10	3	1	2	2	25

* MI indicates mitral insufficiency; MD, mitral diastolic; AI, aortic insufficiency; AS, apical systolic.

TABLE 8.—*Results of Cortisone Treatment of Initial Attack of Rheumatic Carditis*

Onset, Wk.	Total No. Patients	Normal Hearts		Apical Systolic Grade 1	Murmurs Only	Enlarge-ment and Murmurs	Reacti-vation	Fever*	Sed. Rate >15 Mm/Hr.†	Deaths
		No.	Per Cent							
<2	14	12	86	0	1	1	0	6 (2)	5 (1)	0
2-6	27	16	59	3	6	2	1	16 (9)	12 (5)	0
>6	14	1	7	0	7	4	3‡	8 (4)	6 (2)	2
Total	55	29	53	3	14	7	4	30	23	2
<2-6	41	28	68	3	7	3	1	22	17	0

* Numbers in parentheses indicate patients with no sed. rate increase.
† Numbers in parentheses indicate patients with no fever.
‡ One patient treated more than 56 days, other 2 less.

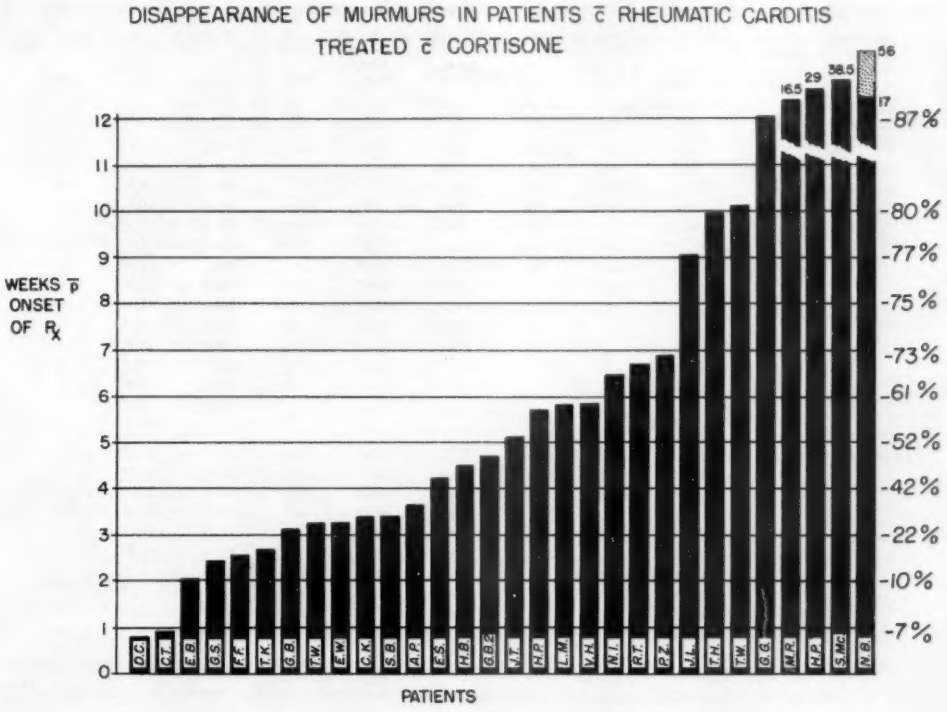
was present in 16% and endocarditis in all. The auscultatory findings indicated the presence of mitral valve lesions in more than 95% of the patients. In 67% they were the only evidence of endocarditis.

The incidence of abnormal cardiovascular findings in the three groups again indicates the increased severity of the illness as it continues for long periods. The percentage of children with cardiac enlargement, congestive failure, pericarditis, and multiple valvular lesion was greatest in the group ill more than six weeks. Similar but less marked differences occurred between the two earlier groups. The incidence of prolonged P-R intervals was only 45%, since usually only one electrocardiogram was obtained prior to therapy (Table 7), but these were not the only electrocardiographic abnormalities, since prolonged Q-T intervals, slurred QRS complexes, and intraventricular heart block were seen also.‡

C. Clinical and Cardiac Changes During Treatment.—At the end of therapy 25 patients had completely normal cardiac find-

‡ Greenman, L.; Danowski, T. S.; Mateer, F. M., and Weigand, F. A.: Unpublished data.

ings; 4 others had Grade 1 mitral systolic bruits. Ten children had significant mitral systolic murmurs, and 2 more, aortic insufficiency. Twelve of the group had cardiac enlargement plus valvular lesions. On discharge all had normal P-R intervals (Tables 1-3). The Figure illustrates the rate at which cardiac murmurs disappeared during and subsequent to therapy in those patients who developed normal clinical cardiac findings. Only 10% of the patients were normal after two weeks of cortisone therapy; 50% after five weeks, and 75% at seven weeks. The remaining 25% returned to normal 9 to 56 weeks after starting treatment, although 90% were normal within 12 weeks.



Individual dosage of cortisone on a per kilogram basis is represented in Table 4. Only one of the five patients receiving 100 mg. per day developed a normal heart, as did one of the two receiving 200 mg. a day. Twenty-five of the 45 patients receiving 300 mg. per day of cortisone had no residual cardiac abnormality. When the 10 in Group 3 are omitted, then 71% developed normal hearts. The end results in the three children receiving higher dosages were one normal heart, one abnormal heart, and one death. The death occurred in R. C., who was admitted after eight months of active rheumatic carditis with severe congestive heart failure and pericarditis. He received 50 mg. of cortisone every 12 hours for three and one-half days and then 100 mg. every three hours, starting the day before death.

Blood pressure measurements were difficult to evaluate because of their variability. However, no patient ended therapy with hypertension, although two of them, R. T. and J. D., had persistent increases to 160/100 and 155/100, respectively, during cortisone administration. P-R intervals in the electrocardiogram returned to normal ranges within three weeks in all patients but those receiving digitalis; in them, seven and eight weeks elapsed. Those who were in failure during treatment had a diuresis while receiving cortisone and sodium-restricted diets. No

patient was in congestive failure at the end of therapy.

Body weight did not change significantly in the groups until increases were noted at the fourth week of therapy in the first two categories and in the fifth week in the children sick for the longest time (Table 9). Body weights ultimately increased by mean figures of 20% to 25% in all groups. Appetites became large, and the later changes in weight were attributed to an increase in flesh, since no visible edema was present.

In the patients who survived, polyarthritis as well as objective joint changes disappeared within one to two days of onset of cortisone therapy. The one exception, M. R., took nine days. It was interesting to see that bed rest prior to onset of steroid treatment would often be associated with disappearance of joint difficulties. Skin rashes disappeared one to eight days after onset of therapy. J. A. was the one exception who took 39 days to clear. Subcutaneous nodules were slow to disappear and did so 7 to 23 days after onset of steroid treatment. Temperatures returned to normal ranges within four hours to three days in all patients but three. In these, a period of 5, 9, and 10 days elapsed. The incidence of recurrent pyrexia has been illustrated in Tables 1-3 and 8.

TABLE 9.—*Body Weight as Percentage of Pretreatment Weight in Patients with Rheumatic Carditis Treated with Cortisone*

Duration of Illness Before Treatment		Group 1, 2 Wk. or Less			Group 2, 2-6 Wk.			Group 3, 6 Wk. or More		
	Wk.	Mean, Per Cent	± Stand. Dev.	(N)	Mean, Per Cent	± Stand. Dev.	(N)	Mean, Per Cent	± Stand. Dev.	(N)
Treatment, Day 1	..	98.2	0.8	4	99.6	1.9	9	98.2	2.8	8
Treatment	1	98.5	3.6	10	99.8	2.8	25	97.2	5.3	15
	2	99.8	4.5	12	100.9	4.2	24	98.5	6.6	14
	3	103.3	6.5	12	103.0	5.5	23	100.3	8.3	13
	4	106.8	7.5*	12	105.9	7.0*	23	104.1	8.7	13
	5	108.6	9.1*	10	110.1	7.8*	21	109.3	9.9*	12
	6	114.6	10.1*	12	113.5	9.5*	22	111.8	7.5*	10
	7	117.9	10.7*	10	118.8	10.0*	17	116.2	7.0*	10
	8	122.5	11.4*	7	121.2	10.4*	16	116.8	5.9*	6
	9	.....	....	..	118.9	11.6*	8	123.0	4.8*	6
	10	.....	....	..	121.3	16.6*	4	126.3	5.6*	4
	11	.....	....	..	134.4	....	2	128.6	6.8*	4
	12	.....	....	..	.....	....	..	129.7	6.0*	4
	13	.....	....	..	.....	....	..	133.3	2.9*	3
	14	.....	....	..	.....	....	..	134.8	2.6*	3
	15	.....	....	..	.....	....	..	135.1	1.6*	3
Post-treatment	1	117.8	11.0*	8	122.5	13.0*	21	120.7	13.7*	12
	2	118.3	10.1*	9	125.0	13.8*	16	120.6	11.0*	8
	3	115.0	6.3*	6	123.3	10.4*	8	125.2	14.0*	4
	4	126.2	15.3*	4	126.6	55.2*	8	122.8	17.6*	3
	5	121.2	7.5*	5	122.8	8.2*	4	112.9	10.1*	4
	6	130.3	....	1	128.1	14.6*	6	127.0	14.3*	5
	7	120.4	6.3*	4	114.2	10.8*	4	115.6	....	1
	8	127.1	9.3*	4	119.8	5.4*	4	.....	....	..
	9	122.9	....	2	138.0	17.4*	3	139.7	....	1
	10	130.0	....	1	120.6	7.5*	4	121.0	....	2
	11	123.3	....	3	120.7	12.2*	5	121.0	....	1
	12	123.5	....	2	128.8	12.0*	3	144.1	....	1

* Deviation from control (Day 1) is statistically significant.

Two patients who were in congestive failure with pericarditis died. They were in the group most seriously ill and were treated early in our study, starting with small amounts of cortisone. One patient (M. S.) had been sick for three months and died after three days of receiving relatively small amounts of the steroid. The other (R. C.) had been ill for eight months and died after five days of cortisone therapy, starting with small amounts.

D. Findings at the End of or Shortly Following Completion of Therapy.—Upon withdrawal of the steroid and transfer to a normal diet transient increases in fever and sedimentation rates were evident in slightly more than half the entire group of patients. It is interesting to note that both were not abnormal at the same time in many children. The rapid subsidence, within a few days or a week, of this laboratory rebound usually suggested that these events did not indicate reactivation of rheumatic fever. With the exception of four patients, it is pertinent to note that there was no recurrence or new considered indicative of active rheumatic fever.

E. End Results.—1. In Relationship to Duration of Illness Prior to Therapy: Significant differences in the results of therapy appear when the outcome is evaluated in each subgroup according to duration of illness prior to treatment. The best results were obtained in patients sick less than two weeks. In that group 86% (12 of 14 patients) had no residual cardiac abnormalities; one was left with a murmur, and one had both cardiac enlargement and murmurs. No one showed evidence of rheumatic fever at end

TABLE 10.—*Results of Cortisone Treatment of Initial Attack of Rheumatic Carditis*

		Cardiac Findings						
		Pretreatment		Result of Treatment				
				Normal				
Onset, Wk.	Age, Yr. (Mean)	Enlarged Heart	Congestive Heart Failure	No.	Per Cent	Murmurs	Apical Systolic Grade 1	Enlarged Heart and Murmur
Cardiac Enlargement at Onset								
<2	7.8	4	4	3	75	0	0	1
2-6	8.4	14	11	6	43	5	1	2
>6	10.1	12	9	1	8	5	0	4*
Total		30	24	10	33	10	1	7
<2-6		18	15	9	50	5	1	3
No Enlargement								
<2	9.1	10	0	9	90	1	0	0
2-6	10.0	13	0	10	77	1	2	0
>6	9.0	2	0	0	0	2	0	0
Total		25	0	19	76	4	2	0
<2-6		23	0	19	83	2	2	..

* Two deaths.

development of joint pains, skin eruptions, subcutaneous nodules, or evidences of carditis in any of these children. Clinically active rheumatic fever was evident, however, in these four patients after completion of therapy. C. S. had been treated for 56 days, E. W. and P. M. for 11 and 10 days, respectively, while D. S. received cortisone for 43 days. They were all retreated but have residual cardiac abnormalities. Following the second course of therapy only one, C. S., of the four developed both fever and sedimentation rate increases; two others, P. M. and E. W., had increases in sedimentation rates alone, while D. S. had neither. These abnormalities were transient and disappeared within one week. They were therefore not of therapy. The intermediate group appears to have a smaller percentage of normal hearts, but this difference is not statistically significant.

In the patients who were sick more than six weeks, the outcome in every respect was worse than in the patients treated earlier. There were fewer normal hearts and more murmurs, cardiac enlargement, reactivations, and deaths. No difference is apparent in temporary increases in fever and sedimentation rates. It is important to note that no patient ended therapy with more evidence of cardiac abnormalities than he had on admission. In a few patients transient murmurs developed during treatment but dis-

appeared before cortisone therapy was discontinued.

2. In Relationship to Cardiac Enlargement: The adverse influence of cardiac enlargement is strikingly demonstrated in Table 9. Although one-third of all the patients with enlargement developed normal hearts, one-half of those treated within the first six weeks showed this improvement. When no enlargement was present prior to therapy, 75% to 90% of the patients had completely normal hearts at final evaluation.

3. In Relationship to Cortisone Dosage: These data have been presented earlier, in Section C.

4. In Relationship to Entire Group: With one exception, follow-up time varied from 3 to 39 months (Tables 1-3). Fifty-three per cent of the entire group had no demonstrable cardiac abnormality by physical examination before and after exercise, teleoroentgenogram with barium swallow, or fluoroscopy. In three patients in the group treated two to six weeks after onset of rheumatic fever the cardiothoracic ratio was reported as 0.51 to 0.53. Since these patients had no murmurs on physical examination even after exercise, normal cardiac sounds without tachycardia, normal fluoroscopic examination for heart size and shape, and somewhat elevated diaphragms by x-ray, we have concluded that they had no definite evidence of organic abnormalities. In contrast to our pretreatment exclusion of patients with apical systolic Grade 1 murmurs, we have listed such children separately when evaluating the results, provided no other abnormality was detected. We are uncertain of its significance. In any event only three of the patients have such a finding. Fourteen children were left with murmurs only and 7 others with enlargement and murmurs.

II. COMPLICATIONS DURING TREATMENT WITH CORTISONE

A. Hyperadrenalism.—All patients receiving these large amounts of hormones for more than two weeks developed moon facies, protuberant abdomens, cervical fat deposits, and mild hirsutism. Acne developed in seven. Striae were evident in 13 patients. In no instance did these findings contraindicate continued treatment. All of them, with the exception of the striae which became lighter, disappeared within several months after therapy was discontinued. One patient (S. B.) developed hematuria and hypertension for an unknown reason after therapy, but this subsided uneventfully.

B. Mental Changes.—One patient only (P. M.) required cessation of therapy because of a toxic psychosis. She was 15 5/12 years old and received 7.8 gm. of cortisone in 37 days following a 10-day course totaling 1.0 gm. Her diet contained 2.5 mEq. of sodium at the time. She had been disturbed about events at home, and during several days became negativistic, depressed, unable to speak, and confused and attempted to commit suicide. She was transferred to a psychiatric hospital and recovered completely after two months. Balance studies and blood analyses were done prior to the onset of the toxic psychosis so that we are able to say that this event was not associated with abnormally low serum potassium concentrations or negative external balances of potassium. In addition there was no evidence of hyponatremia. More than three years later she is apparently well mentally.

Homesickness was a frequent early problem. Many of the children became cheerful and active as they improved. Those who did not do well did not demonstrate euphoria.

C. Infection.—Beta hemolytic streptococci were isolated in throat cultures from 16 of the children after several weeks of penicillin therapy. They were asymptomatic at the time. Several others developed bronchopneumonia with upper respiratory infections. Measles occurred in two of the other children; continued treatment with cortisone did not affect the course of this illness.

D. Abdominal Distention.—Four patients developed temporary marked abdominal distention during cortisone therapy Two had gastrointestinal series and stool examinations without detection of local lesions. The complaints disappeared as treatment continued.

COMMENT

It seems very likely that the present regimen, which included cortisone in large amounts, diets rigidly limited in sodium and high in potassium, penicillin, and bed rest, has beneficially affected the rheumatic state itself and has prevented or reduced the incidence of clinically recognizable residual cardiac abnormalities. Although the mechanism of this action is not clear, it is reasonable to suggest that this steroid, in sufficiently large amounts, suppresses the inflammatory reaction of rheumatic fever. The substance must be given until the illness has run its course if flare-ups are not to occur. The exact duration of treatment must be left uncertain at this time, for in some patients several weeks may be sufficient, in others months, and in still others years may be needed.

Duration of illness prior to therapy was an important factor in determining the outcome. For example, almost 90% of the children treated within two weeks of onset of clinically evident carditis have no recognizable residual cardiac abnormalities, while only 7% of those treated after six weeks of illness are normal. The group treated between two and six weeks after onset resembles those treated within the first two weeks. These data are consonant with the concept that a lesion may become irreversible after a sufficient interval and that early therapy offers the best chance of preventing residual damage. It also clearly demonstrates the necessity for describing duration of illness prior to treatment in evaluating results. The importance of duration of disease before treatment has also been suggested by Barnes,[5] Bywaters,[12] Kelley,[31] Massell,[36] and Wilson [46] and their co-workers, but none had enough patients to prove the concept. Obviously patients with residues of previous attacks do not resolve such lesions even if they respond well to the treatment of subsequent attacks.

The amounts of cortisone administered and the duration of therapy are two other important considerations. The amounts suggested in the present schedule are in keeping with experimental and clinical observations that large amounts of this hormone are required to inhibit experimental inflammatory lesions and that cortisone is a suppressive rather than a curative agent. Many experimental and clinical observations now exist, demonstrating the necessity for large doses of cortisone (6.2-50 mg. per kilogram of body weight per day) to suppress inflammatory reactions.§

It is not possible at present to be certain that we have arrived at the optimum dose or length of treatment. Indeed, two of our patients with chronically active rheumatic fever (not presented here) were treated with cortisone continuously for more than one year to prevent reactivation when cortisone was discontinued. Taran, who has reported unsatisfactory results with a similar group of chronically active patients, gave smaller amounts for shorter intervals.[59] In addition, there is no assurance that an eight-hour interval is optimal at this dosage of cortisone. In brief, it is our belief that the present therapy is effective but that a sufficient amount of hormone must be given early enough and for long enough interval for the illness to run its course. We have no eivdence that cortisone has shortened the duration of this disease.‖

In the absence of specific control data it is not possible to decide which parts of the regimen employed were most important. The penicillin was necessary for treatment of bacterial infections and for prophylaxis to prevent second attacks of rheumatic fever. The diet was very low in sodium and high in potassium and supplemented by iron and vitamins. The low-sodium-high-potassium intake may well have influenced endogenous adrenal cortex function and perhaps minimized the suppressive effects of exogenous cortisone. In addition, this low sodium intake would seem to be a major reason for the diuresis and absence of increased congestive failure in these patients. Even though hyponatremia did not appear in the children presented, it is always a hazard when sodium is rigidly restricted. A high potassium intake

§ References 54-58.

‖ References 60 and 61.

is usually necessary when cortisone is administered. Bed rest was also enforced. Perhaps none of these factors alone would yield similar responses, but the entire combination is needed.

There are a number of questions which make it difficult to be certain whether any regimen prevents residual cardiac abnormalities. They would best be answered by alternate control data if data on a sufficient number of patients are accumulated so that the groups become comparable. In any event, microscopic examinations of valve leaflets and myocardium certainly would be necessary. The assessment of residual cardiac abnormalities in patients presenting themselves with previous rheumatic heart disease may be insurmountable unless additional valvular lesions are identified. Massell has recently reviewed the published data concerning hormone therapy of this illness.[62] It is not known whether there has been a change in incidence of residual cardiac abnormalities in untreated patients with only one attack of rheumatic carditis. Although the data showing the decrease in mortality are convincing, they may result from improved therapy of infections, disease, and congestive failure. In children it is known that the incidence and severity of cardiac damage increase directly with the frequency of rheumatic fever. It is difficult to find adequate data in the literature to clarify this point; although that of R. Ash,¶ E. F. Bland,[65] C. F. Coombs,[66] W. D. Stroud,[67] and May Wilson [68] suggest that 65% to 100% of children have residual cardiac abnormalities after an initial attack of clinically evident rheumatic carditis. Our two patients G. B. and T. W. with subsequent bouts of carditis lend weight to the beneficial results of the present regimen, since they have no clinical evidence of residual cardiac damage. However, the rest of our group had only one attack.

Duration of follow-up is another important factor in considering our results. Cardiac findings may change as patients mature.# Statistics on adults are of no help, since they have a far better outlook.[73]

One of our major unexplained problems is the brief fever and increase in sedimentation rate that occurred at the end of therapy. These may represent the laboratory rebound that is mentioned in the literature. Only four of our children had clinical rebounds, and they were successfully retreated.

There is no satisfactory method for predicting which patients will reactivate after cessation of treatment; for that reason it is conceivable that therapy at adequate dosage may have to be continued for six months, one year, or more in some persons. There is no way of predicting the effects of such therapy on the patents' own adrenals, and the best manner of discontinuing treatment still must be decided.* It may be advisable to administer cortisone to all children with rheumatic fever as soon as the diagnosis is established. Preferably the steroid should be given before clinically evident carditis is recognized in order to provide the best opportunity for prevention of residual cardiac damage.

SUMMARY

Fifty-three children with clinically recognizable first attacks of rheumatic carditis have been treated with a regimen employing cortisone in larger amounts and for longer periods than usually administered, plus penicillin, a very low-sodium-high-potassium diet, and bed rest. There has been a low incidence of residual cardiac abnormalities in those treated within six weeks of onset and especially in those treated within two weeks. The safety of the regimen is illustrated, and the principle of large dosage for prolonged periods as well as early therapy is discussed and emphasized.

ADDENDUM

Since submission of our paper the following report has appeared: Joint Report of the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investi-

¶ References 63 and 64.

References 69-72.

* References 74 and 75.

gators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association: The Treatment of Acute Rheumatic Fever in Children; A Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin, Circulation **11**:343 (March) 1955. The paper indicates that cortisone and corticotropin (ACTH) were not more effective than salicylates in controlling the clinical manifestations and anatomical residua of rheumatic fever. Their therapeutic program differed from ours, since we gave cortisone orally in much larger amounts for longer periods of time.

Dr. E. R. McCluskey, Professor of Pediatrics and Head of the Department, as well as many staff men, nurses, residents, fellows, and technicians, cooperated in this study. Dr. Frank Gregg made some patients available at the onset of the study and was instrumental in obtaining the Kiwanis grant.

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Cortisone Therapy of Initial Attacks of Rheumatic Carditis

II. Laboratory Findings

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INTRODUCTION

In the preceding paper the clinical effects of a regimen of cortisone, bed rest, antibiotics, and diets stringently limited in sodium and high in potassium have been described in 53 children in initial attacks of rheumatic carditis.[1] The clinical response suggested that such treatment was beneficial and that the treatment program suppressed the disease process. The present paper describes in detail the changes in the routine bacteriological, hematological, biochemical, and related studies conducted prior to, during, and following therapy.

METHODS

In addition to determinations of sedimentation rates, blood cell counts, and urinalyses, nose and throat swabs were cultured for predominant organisms, and antistreptolysin O titers were determined.[2] The biochemical studies included measurements of fasting levels of nonprotein nitrogen and sugar in venous blood and of total CO_2 content, chloride, sodium, potassium, total protein, albumin, globulin, cholesterol, and phosphorus in serum.[3]

As in the case of the clinical course, the findings are divided when indicated in accordance with the duration of the illness prior to therapy, i. e., less than two weeks, two to six weeks, and more than six weeks.

RESULTS

A. Hemolytic Streptococci.—Eight of the patients had β hemolytic streptococci in their nasopharynx on admission. Subsequently 16 more of the total of 55 patients had β hemolytic streptococci isolated from their throats one or more times during hospitalization while on both cortisone and prophylactic oral penicillin therapy (100,000 units three times a day between meals). The latter persons had been free of this organism for at least one week prior to the positive culture. None of these patients had a flare-up of the disease, any new clinical symptomatology, or an increase in antistreptolysin O titers at the time the cultures became positive.

B. Antistreptolysin O Titers (Normal Less Than 250 Units per Milliliter).—Even though only eight of the 53 children had β hemolytic streptococci in their nasopharyngeal cultures on admission, 80% had antistreptolysin O titers of 250 or more units per milliliter. The highest values were 2500. These initial values substantiate the impression that the patients had been exposed to β hemolytic streptococci prior to admission. There was no direct correlation with severity of the illness. Mean titers are shown in Table 1. It is evident that by the end of the sixth week three-quarters of the children had antistreptolysin O titers below 250 units per milliliter.

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TABLE 1.—*Antistreptolysin O Titer*

	Wk.	Entire Group: Mean, U./Ml.	± Stand. Dev.	(N)	No. < 250, U./Ml.
Pretreatment	..	682	542	40	8
Treatment	1	635	359	8	0
	2	356	217 *	22	6
	3	279	225 *	10	6
	4	255	222 *	32	16
	5	315	300 *	10	6
	6	165	71 *	26	19
	7	217	196 *	11	7
	8	170	169 *	20	16
	9	143	76	4	3
	10	140	36 *	6	6
Post-treatment	1	134	42 *	14	14
	2	127	124 *	13	12
	3	135	55	4	4

* Deviation from pretreatment mean is statistically significant.

No differences in rates of return to normal were evident in the three groups. It is to be noted that only one child, R. C., had an elevated value at completion of treatment; four weeks afterward, however, this patient was also within the normal range. As noted above, no patient had a secondary rise in titer even though hemolytic streptococci were again isolated by culture.

C. Wintrobe Sedimentation Rates.—Wintrobe sedimentation rates corrected for the hematocrit reading are presented in Table 2. Almost all patients had increased rates prior to therapy. The highest percentage of normal sedimentation rates (15 mm. or less per hour) was present in the patients who were ill longest prior to treatment, i. e., six weeks or more. Significant decreases in mean values occurred throughout steroid administration in all groups. At the end of four weeks, 92%-100% of all children had normal rates.

When cortisone was discontinued, Group 1 remained within normal limits, although several patients had minor increases in sedimentation rate; similar slight increases occurred in Group 2 but subsided after one week. In Group 3, however, the mean values usually rose outside the normal range, with only a small percentage of persons remaining below 15 mm. per hour (Table 2).

D. Blood and Urine Data.—Hemoglobin values (average 10.7 gm. per 100 cc.) and red blood cell counts (average 3,700,000

TABLE 2.—*Wintrobe Sedimentation Rate*

		Duration of Illness Before Treatment: Group 1, 2 Wk. or Less				Group 2, 2-6 Wk.				Group 3, 6 Wk. or More			
	Wk.	Mean, Mm./Hr.	± Stand. Dev.	(N)	No. < 16, Mm./Hr.	Mean, Mm./Hr.	± Stand. Dev.	(N)	No. < 16, Mm./Hr.	Mean, Mm./Hr.	± Stand. Dev.	(N)	No. < 16, Mm./Hr.
Pretreatment	..	36.1	14.3	14	1	29.0	11.1	27	3	28.4	18.4	16	6
Treatment	1	24.8	14.6	14	4	21.8	12.6 *	25	8	18.8	14.3	14	6
	2	10.2	6.1 *	13	9	10.5	10.9 *	24	18	8.5	7.5 *	13	10
	3	10.0	6.7 *	12	9	7.8	7.0 *	23	20	6.6	2.6 *	14	13
	4	8.2	6.1 *	13	12	4.6	4.4 *	23	22	3.2	2.3 *	12	12
	5	9.6	8.3 *	12	8	5.1	4.9 *	21	20	6.1	4.6 *	8	8
	6	8.5	6.7 *	13	11	6.2	5.6 *	22	20	6.0	7.1 *	11	9
	7	10.0	6.8 *	10	8	9.8	11.1 *	19	15	6.7	6.3 *	9	8
	8	8.0	5.7 *	7	6	10.7	10.7 *	19	13	6.5	5.3 *	6	6
	9	....	....	..	..	6.8	7.6 *	8	6	7.8	6.0 *	6	5
	10	....	....	..	..	6.0	6.7 *	4	3	20.0	6.9	4	1
	11	....	....	..	..	....	....	..	..	12.0	7.1	4	2
	12	....	....	..	..	....	....	..	..	18.3	8.0	3	1
	13	....	....	..	..	....	....	..	..	18.5	2.1	2	0
	14	....	....	..	..	....	....	..	..	18.3	2.9	3	1
	15	....	....	..	..	....	....	..	..	12.0	4.4	3	3
Post-treatment	1	10.8	9.3 *	11	8	17.3	13.5 *	23	12	15.5	13.3 *	13	7
	2	11.3	7.1 *	9	5	13.8	10.8 *	18	12	18.2	15.6	11	7
	3	11.0	8.5 *	2	1	13.0	5.6 *	6	4	19.5	20.5	2	1
	4	11.7	11.0 *	3	2	15.2	6.4 *	5	3	22.5	11.5	6	2
	5	11.2	8.7	4	3	10.5	5.6 *	4	3	12.7	9.4	3	1
	6	....	....	..	..	12.8	10.2 *	4	3	10.6	5.4 *	5	4

* Deviation from control mean pretreatment is statistically significant.

TABLE 3.—*Comparison of Serum Constituents Between Healthy Children and Patients Prior to Cortisone Therapy of Initial Attack of Rheumatic Carditis*

	Healthy Children			Rheumatic Carditis, Duration of Illness											
				Group 1, Less Than 2 Wk.				Group 2, 2-6 Wk.				Group 3, 6 or More Wk.			
Serum Constituent	Mean	± Stand. Dev.	(N)	Mean	± Stand. Dev.	(N)	P for T Test	Mean	± Stand. Dev.	(N)	P for T Test	Mean	± Stand. Dev.	(N)	P for T Test
HCO_3, mEq./L.	23.1	1.3	125	22.8	2.6	12	0.53	22.4	2.2	19	0.06	21.1	2.8*	15	<0.0001
Cl, mEq./L.	103.3	3.0	106	98.1	4.9*	12	<0.0001	97.8	4.0*	23	<0.0001	99.6	4.6*	16	<0.0001
Na, mEq./L.	144	3	106	141	7 *	12	0.012	141	4 *	21	0.0006	140	6 *	14	0.0003
K, mEq./L.	4.4	0.4	142	4.8	0.7*	12	0.0007	4.9	0.5*	22	<0.0001	4.8	0.6*	14	0.0003
PO_4, mg./100 cc.	4.8	0.4	65‡	5.2†	0.8*	15	0.004	....	...	..	.....	....	...	..	.....
T.P., gm./100 cc.	7.3	0.6	49	7.2	0.6	13	0.56	7.4	0.8	23	0.60	7.0	1.0	14	0.26
Alb., gm./100 cc.	4.3	0.6	47	3.1	0.5*	12	<0.0001	3.0	0.6*	23	<0.0001	3.2	0.6*	10	<0.0001
Glob., gm./100 cc.	3.0	0.6	47	4.1	0.8*	12	<0.0001	4.4	0.8*	23	<0.0001	4.0	1.2*	9	<0.0001
Chol., mg./100 cc.	229	42	105	199 †	56 *	9	0.048	....	...	..	.....	....	...	..	.....

* Deviation from healthy children is statistically significant
† Entire group.
‡ Age 5.5 to 12.49 yr.

per cubic millimeter) were low on admission. There were patients with normal values in both categories; however, the low readings rose to normal as treatment progressed. At the end of therapy, red blood cell counts averaged 4,000,000 or more per cubic millimeter. Comparably greater rises to 13.3 gm. per 100 cc. were recorded in the hemoglobin values even though the reduction in hemoglobin from normal on admission was proportionately greater than that in the red cell count. The responses in the three groups paralleled each other closely. At the end of therapy there were minor decreases of hemoglobin in Groups 1 and 2, although Group 3 was the only one in which low values were noted.

There was a slight leucocytosis (mean of 12,000 per cubic millimeter), with a minor increase in polymorphonuclear neutrophiles (74%) on admission. The total white blood cell count levels fell slowly to normal (less than 10,000 per cubic millimeter) during the end of therapy in Groups 1 and 2. Blood neutrophiles decreased somewhat more rapidly than the

TABLE 4.—*Blood N. P. N.*

		Duration of Illness Before Treatment											
		Group 1, 2 Wk. or Less				Group 2, 2-6 Wk.				Group 3, 6 Wk. or More			
	Wk.	Mean, Mg./ 100 Cc.	± Stand. Dev.	(N)	No. >39, Mg./ 100 Cc.	Mean, Mg./ 100 Cc.	± Stand. Dev.	(N)	No. >39, Mg./ 100 Cc.	Mean, Mg./ 100 Cc.	± Stand. Dev.	(N)	No. >39, Mg./ 100 Cc.
Pretreatment	..	32	11	14	3	34	5	27	2	35	9	16	4
Treatment	1	36	7	14	4	35	4	27	2	34	4	10	1
	2	35	4	14	1	36	5	27	4	37	5	15	3
	3	33	4	11	1	36	5	23	4	35	5	12	2
	4	35	2	13	0	35	4	24	1	36	5	13	3
	5	36	5	11	2	35	5	21	3	36	6	10	4
	6	34	5	13	1	34	4	22	2	32	5	10	1
	7	32	4	11	1	33	5	19	1	31	5	11	0
	8	29	3	8	0	33	4	16	1	29	3	7	0
	9	..	..	..	..	31	4	9	1	33	4	6	0
	10	..	..	..	..	29	2	4	0	32	4	5	0
	11	..	..	..	..	..	..	..	..	31	4	4	0
Post-treatment	1	32	7	7	1	30	4 *	24	0	27	7	12	0
	2	26	4	7	0	29	5 *	9	0	29	5	9	0
	3	26	4	2	0	30	5	5	0	28	2	4	0
	4	29	4	7	0	32	2	3	0	25	1	2	0
	5	..	..	..	..	30	5	2	0	26	1	2	0
	6	..	..	..	..	28	5	3	0	28	3	5	0

* Deviation from pretreatment mean is statistically significant.

total white cell count and were normal prior to cessation of treatment (less than 70%). In Group 3, however, there was a definite increase at the end of the first week to a mean value of 15,200 per cubic millimeter. The levels were down to pretreatment at the end of five weeks, however, and within normal ranges at the end of treatment. Blood neutrophiles paralleled this response.

Almost half the patients had minor degrees of proteinuria prior to therapy. None was greater than 2+, and none had hematuria or casts at this time. As treatment continued the proteinuria decreased or disappeared.

E. Blood and Serum Constituents,—Tables 3 and 4 show the whole-blood nonprotein nitrogen levels and the total protein, albumin, globulin, serum bicarbonate, chloride, sodium, potassium, phosphorus, and cholesterol values in this group of patients prior to therapy compared with those of a group of healthy children at a children's home in Pittsburgh. The important differences are (1) a lower serum bicarbonate in the patients sick six or more weeks, (2) abnormally low serum chloride, sodium, albumin, and cholesterol values in all groups, (3) elevated serum potassium, phosphate, and globulin concentrations.

Blood nonprotein nitrogen concentrations (Table 4) indicate the normal ranges of this constituent prior to, during, and after therapy. There were a number of children with elevated levels before and, sporadically, during treatment. At the end only one patient had a transient minor increase in nonprotein nitrogen concentration. The original increases reflected a combination of congestive failure, dehydration, and tissue breakdown from illness. The changes during cortisone treatment may well have mirrored the increase in turnover of nitrogen associated with administration of this steroid.

Fasting blood sugars were within the normal ranges and did not differ among the groups (mean 88 mg. per 100 cc.). They did not rise significantly and in a few instances seemed to fall slightly during and after treatment. No patient developed glycosuria. Urinalyses were usually done at one-week intervals.

Serum total proteins were within normal limits in all groups (mean of 7.3 gm. per

TABLE 5.—*Serum Albumin*

		Duration of Illness Before Treatment											
		Group 1, 2 Wk. or Less				Group 2, 2-6 Wk.				Group 3, 6 Wk. or More			
	Wk.	Mean, Gm./ 100 Cc.	± Stand. Dev.	(N)	No. >3.4, Gm./ 100 Cc.	Mean, Gm./ 100 Cc.	± Stand. Dev.	(N)	No. >3.4, Gm./ 100 Cc.	Mean, Gm./ 100 Cc.	± Stand. Dev.	(N)	No. >3.4, Gm./ 100 Cc.
Pretreatment	..	3.1	0.5	12	1	3.0	0.6	23	4	3.2	0.6	10	4
Treatment	1	3.5	0.3 *	12	5	3.2	0.4	23	6	3.4	0.5	9	4
	2	3.5	0.4 *	12	7	3.4	0.5 *	21	10	3.3	0.8	9	3
	3	3.8	0.4 *	12	11	3.7	0.4 *	23	16	3.5	0.4	12	7
	4	3.8	0.4 *	12	10	3.7	0.6 *	20	15	3.5	0.4	12	6
	5	3.9	0.3 *	11	11	3.7	0.3 *	18	15	3.5	0.4	7	4
	6	4.0	0.3 *	12	12	3.8	0.4 *	22	19	3.6	0.3	9	5
	7	3.8	0.3 *	10	8	3.9	0.1 *	18	16	3.5	0.5	8	5
	8	3.9	0.2 *	7	7	3.8	0.2 *	17	13	3.7	0.3 *	7	6
	9	...	...	..	..	3.6	0.1 *	6	6	3.7	0.2	6	5
	10	...	...	..	..	3.6	0.2 *	4	3	3.6	0.3	5	4
	11	...	...	..	..	...	...	..	..	3.5	0.2	3	2
Post-treatment	1	3.7	0.3 *	6	5	3.6	0.2 *	20	14	3.6	0.2	9	7
	2	3.7	0.7 *	7	5	3.7	0.4 *	11	9	3.6	0.2	9	6
	3	3.8	0.2 *	4	4	4.5	0.5 *	5	3	3.6	0.5	4	2
	4	3.8	0.6 *	3	2	3.9	0.4 *	4	4	3.4	0.3	4	1
	5	3.6	0.4	2	1	...	...	..	..	3.6	0.1	2	2
	6	...	...	..	..	4.4	0.5 *	3	3	4.0	0.3 *	5	5

* Deviation from pretreatment mean is statistically significant.

TABLE 6.—*Serum Globulin*

		Duration of Illness Before Treatment											
		Group 1, 2 Wk. or Less				Group 2, 2-6 Wk.				Group 3, 6 Wk. or More			
	Wk.	Mean, Gm./ 100 Cc.	± Stand. Dev.	(N)	No. < 3.3, Gm./ 100 Cc.	Mean, Gm./ 100 Cc.	± Stand. Dev.	(N)	No. < 3.3, Gm./ 100 Cc.	Mean, Gm./ 100 Cc.	± Stand. Dev.	(N)	No. < 3.3, Gm./ 100 Cc.
Pretreatment	..	4.1	0.8	12	2	4.4	0.8	23	2	4.0	1.2	9	3
Treatment	1	3.6	0.7	12	4	3.8	0.6 *	23	1	3.6	0.9	9	3
	2	3.0	0.9 *	12	7	3.3	0.5 *	21	10	3.2	0.6	9	4
	3	2.7	0.5 *	12	10	2.9	0.4 *	23	16	2.9	0.6 *	12	10
	4	2.6	0.7 *	12	11	2.7	0.5 *	20	18	3.0	0.6 *	12	9
	5	2.6	0.6 *	11	10	2.8	0.5 *	18	14	2.7	0.4 *	8	8
	6	2.7	0.4 *	12	11	2.8	0.5 *	22	18	2.7	0.6 *	9	7
	7	2.7	0.8 *	10	8	2.7	0.3 *	18	17	2.7	0.5 *	7	6
	8	2.5	0.5 *	7	6	2.8	0.4 *	17	15	2.5	0.3 *	7	7
	9	....	....	..	..	2.9	0.7 *	6	4	2.7	0.4 *	6	5
	10	....	....	..	..	2.5	0.6 *	4	4	2.7	0.6 *	5	4
	11	....	....	..	..	....	....	..	..	2.5	0.2 *	3	3
Post-treatment	1	2.8	0.7 *	6	5	2.8	0.6 *	19	15	2.5	0.5 *	9	9
	2	2.6	0.8 *	7	6	2.6	0.4 *	10	9	2.9	0.5 *	9	8
	3	2.7	0.5 *	4	3	2.8	0.3 *	4	4	3.0	0.6 *	4	3
	4	2.4	0.8	3	3	2.8	0.2 *	4	4	3.2	0.6 *	4	3
	5	2.2	0.3 *	2	2	....	....	..	..	3.2	0.2	2	1
	6	....	....	..	..	2.4	0.2 *	3	3	2.8	0.6 *	5	4

* Deviation from pretreatment mean is statistically significant.

100 cc.) and fell progressively during treatment but not to abnormally low values (mean of 6.4 gm. per 100 cc.). Serum albumin concentrations (Table 5) were low at the start and rose during therapy. However, the rises were earlier and persisted longer in the first two groups. The values did not increase significantly in Group 3 until there was a temporary rise on the eighth week. Few values above 4.0 gm. per 100 cc. were evident. Serum globulin levels (Table 6) were strikingly elevated in all groups before cortisone administration. The fall in serum total proteins reflected the changes in globulins. Globulins gradually decreased and were 3.0 gm. per 100 cc. or less two to three

TABLE 7.—*Serum Bicarbonate*

		Duration of Illness Before Treatment											
		Group 1, 2 Wk. or Less				Group 2, 2-6 Wk.				Group 3, 6 Wk. or More			
	Wk.	Mean, mEq./ L.	± Stand. Dev.	(N)	No. > 25.7, mEq./ L.	Mean, mEq./ L.	± Stand. Dev.	(N)	No. > 25.7, mEq./ L.	Mean, mEq./ L.	± Stand. Dev.	(N)	No. > 25.7, mEq./ L.
Pretreatment	..	22.8	2.6	12	2	22.4	2.2	19	0	21.1	2.8	15	0
Treatment	1	25.8	2.7 *	9	7	24.7	1.8 *	18	6	25.5	2.9 *	8	4
	2	26.5	2.2 *	10	7	26.2	2.8 *	21	12	25.2	1.8 *	13	4
	3	26.3	1.8 *	8	4	25.7	2.2 *	17	8	25.3	2.2 *	10	4
	4	26.1	1.6 *	10	5	26.4	3.0 *	15	9	25.6	2.0 *	11	5
	5	26.0	1.8 *	8	5	26.4	2.7 *	13	8	26.0	3.3 *	8	3
	6	25.5	2.0 *	12	6	25.2	2.5 *	16	8	25.3	1.9 *	9	3
	7	25.3	2.1 *	10	5	25.5	2.7 *	13	6	24.2	2.8 *	9	2
	8	25.3	2.0	6	3	24.1	2.2 *	14	3	24.6	2.8 *	5	3
	9	....	....	..	..	24.4	2.5 *	8	3	23.0	1.9	5	0
	10	....	....	..	..	23.7	1.0	4	3	22.4	1.3	4	0
	11	....	....	..	..	....	....	..	..	21.4	1.9	3	0
Post-treatment	1	21.8	1.8	6	0	22.5	3.3	15	2	23.5	3.2	11	2
	2	20.7	2.3	3	0	20.7	3.0	6	0	22.0	2.0	8	0
	3	....	....	..	..	23.8	2.3	4	1	23.2	2.4	3	1
	4	....	....	..	..	24.0	1.4	4	0	21.6	1.8	2	0
	5	....	....	..	..	23.6	0.9	2	0	21.4	1.8	2	0
	6	....	....	..	..	23.3	1.2	3	0	....	....	..	..

* Deviation from pretreatment mean is statistically significant.

TABLE 8.—*Serum Chloride*

		Duration of Illness Before Treatment											
		Group 1, 2 Wk. or Less				Group 2, 2-6 Wk.				Group 3, 6 Wk. or More			
	Wk.	Mean, mEq./L.	± Stand. Dev.	(N)	No. < 96.0, mEq./L.	Mean, mEq./L.	± Stand. Dev.	(N)	No. < 96.0, mEq./L.	Mean, mEq./L.	± Stand. Dev.	(N)	No. < 96.0, mEq./L.
Pretreatment	..	98.1	4.9	12	3	97.8	4.0	23	8	99.6	4.6	16	4
Treatment	1	97.2	4.0	11	3	98.1	3.4	19	8	97.3	4.7	9	2
	2	96.3	3.6	12	5	95.6	4.3	21	13	95.7	6.1	13	5
	3	96.5	3.0	10	3	95.6	3.4	17	9	97.5	4.0	10	3
	4	95.6	3.3	11	8	95.9	4.2	16	10	97.4	4.5	11	5
	5	95.3	4.6	10	6	95.9	3.8	13	7	97.1	4.0	9	3
	6	96.2	4.8	12	4	96.5	3.1	16	5	98.0	4.1	9	2
	7	95.4	3.6	10	5	96.8	3.4	13	5	99.2	4.0	9	2
	8	98.8	4.3	6	1	97.5	3.2	14	5	98.7	1.2	5	0
	9	....	...	..	..	98.3	3.0	8	1	98.0	1.3	5	0
	10	....	...	..	..	97.0	2.7	4	1	99.0	2.1	4	0
	11	....	...	..	..	....	...	..	..	95.4	5.5	3	1
Post-treatment	1	98.0	4.5	6	2	99.8	3.6	15	2	100.0	4.1	11	1
	2	100.1	4.0	3	0	100.6	2.4	7	0	100.9	2.3	8	0
	3	....	...	..	..	100.0	2.0	4	0	100.3	4.2	3	0
	4	104.1	4.5	3	0	98.8	4.9	6	0	99.5	4.0	2	0
	5	103.2	4.9	2	0	100.9	3.4	3	0	103.4	0.6	2	0
	6	....	...	..	..	103.8	6.6 *	3	0	103.2	0.0	2	0

* Deviation from pretreatment mean is statistically significant.

weeks after onset of treatment. They did not become abnormal after therapy was discontinued.

Serum Electrolytes and Cholesterol.—The concentration of all the electrolytes measured with the exception of sodium changed significantly during treatment. The changes in bicarbonate (Table 7) and chloride (Table 8) are the usual ones noted during cortisone treatment. Serum bicarbonate rose above 25.7 mEq. per liter in 69% of the patients and then returned to normal after cessation of steroid medication. Serum chloride values decreased during cortisone administration, but not significantly from initial values, since they were low at the onset. However, 73% of the patients developed chloride concentrations below 96.0 mEq. per liter. These concentrations increased to normal when the medication was discontinued. No patient developed alkalotic tetany.

TABLE 9.—*Serum Sodium*

		Duration of Illness Before Treatment								
		Group 1, 2 Wk. or Less			Group 2, 2-6 Wk.			Group 3, 6 Wk. or More		
	Wk.	Mean, mEq./L.	± Stand. Dev.	(N)	Mean, mEq./L.	± Stand. Dev.	(N)	Mean, mEq./L.	± Stand. Dev.	(N)
Pretreatment	..	141	7	12	141	4	21	140	6	14
Treatment	1	141	4	10	142	4	19	140	3	9
	2	140	4	12	140	3	21	139	3	13
	3	138	8	10	141	2	17	140	4	10
	3	141	5	8	141	5	17	141	3	11
	5	141	3	10	141	5	14	140	4	8
	6	143	4	12	142	4	18	142	4	9
	7	145	8	10	142	3	12	142	3	8
	8	146	8	6	142	4	14	141	6	5
	9	...	..	..	141	2	7	140	3	5
	10	...	..	..	138	5	4	137	3	4
Post-treatment	1	142	2	4	142	3	15	140	4	10
	2	141	6	3	142	2	7	139	8	7
	3	...	..	..	144	5	3	...	..	..
	4	144	5	3	143	6	5	...	..	..
	5	...	..	..	...	..	..	...	..	..
	6	...	..	..	145	4	3	...	..	..

Serum sodium concentrations (Table 9) did not change during or immediately following treatment despite the rigid sodium limitation of the diet.

Potassium changes in Table 10 describe a gradual downward trend, but no group fell outside the normal ranges. A significant decrease was first evident at the seventh week in the last two groups. No patient had a serum potassium level as low as 3.0 mEq. per liter. Potassium concentrations between 3.1 and 3.4 mEq. per liter appeared during treatment in only 8 of the 307 analyses.

TABLE 10.—*Serum Potassium*

		Duration of Illness Before Treatment											
		Group 1, 2 Wk. or Less				Group 2, 2-6 Wk.				Group 3, 6 Wk. or More			
	Wk.	Mean, mEq./L.	± Stand. Dev.	(N)	No. < 3.5, mEq./L.	Mean, mEq./L.	± Stand. Dev.	(N)	No. < 3.5, mEq./L.	Mean, mEq./L.	± Stand. Dev.	(N)	No. < 3.5, mEq./L.
Pretreatment	..	4.8	0.7	12	0	4.9	0.5	22	0	4.8	0.6	14	0
Treatment	1	4.9	0.4	10	0	4.7	0.6	18	1	4.5	0.7	9	0
	2	4.5	0.5	12	0	5.0	0.6	19	0	4.7	0.5	13	0
	3	4.5	0.4	10	0	4.7	0.6	17	0	4.6	0.5	11	0
	4	4.2	0.6 *	11	1	4.6	0.6	18	1	4.5	0.6	11	0
	5	4.5	0.4	10	0	4.7	0.6	13	1	4.5	0.5	9	0
	6	4.7	0.7	12	0	4.7	0.6	17	0	4.4	0.5	9	0
	7	4.3	0.4	10	1	4.5	0.5 *	13	0	4.3	0.2 *	8	0
	8	4.2	0.6	6	1	4.3	0.4 *	13	0	4.2	0.6	5	1
	9	...	...	..	..	4.4	0.6 *	7	0	4.2	0.2 *	5	0
	10	...	...	..	..	4.2	0.5 *	4	0	4.2	0.4	4	0
	11	...	...	..	..	...	...	..	..	4.0	0.4 *	3	0
Post-treatment	1	4.1	0.7	6	0	4.3	0.6 *	14	1	4.2	0.6 *	11	2
	2	4.3	0.3	3	0	4.2	0.4 *	7	0	4.2	0.5 *	8	0
	3	...	...	..	..	4.1	0.1 *	3	0	4.1	0.3	3	0
	4	4.4	0.5	3	0	4.4	0.4	5	0	...	...	..	..
	5	4.5	0.3	2	0	4.4	0.4	2	0	...	...	..	..
	6	...	...	..	..	4.4	0.3	3	0	4.7	0.6	3	0

* Deviation from pretreatment mean is statistically significant.

These lower values usually did not persist despite unchanged therapy. Three patients in Group 1, three in Group 2, and two in Group 3 developed such values. One of these occurred after 12 weeks and another one after 16 weeks of cortisone therapy. No abnormal electrocardiographic changes or other signs of potassium depletion occurred.

Serum inorganic phosphorus was slightly increased to a mean of 5.2 mg. per 100 cc. on admission and decreased significantly during the second to sixth weeks of cortisone therapy (mean 4.6 mg. per 100 cc.). Serum cholesterol averaged 199 mg. per 100 cc. on admission and increased gradually during treatment to a mean of 308 mg. per 100 cc.

COMMENT

The safety with which a regimen of cortisone and diets rigidly limited in sodium and high in potassium can be given to a group of children with acute rheumatic carditis has been demonstrated. Only minor changes, uninfluenced by duration of illness prior to treatment, were observed in the concentrations of the electrolytes and crystalloids measured.

The pretreatment findings undoubtedly reflect the combination of illness and decreased dietary intake. Large changes in total amounts of materials may have been masked, however, by minor changes in concentration. This would occur if body water changed equivalently. One important reason for a low extracellular sodium value may have been an internal shift of sodium into cells when these patients were ill.[4] Potassium may have moved out as well. The increased potassium levels, as well as the high phosphorous levels, presumably reflect a new steady state, or they could represent the effects of renal failure as shown by azotemia in 17% of the initial values. The absence of a hypochloremic alkalosis when these patients were admitted to the hospital does not substantiate cellular

potassium deficits, but we have seen other examples, such as diabetic acidosis, carbohydrate starvation, renal failure, and diarrhea where this specific change does not occur. Presumably in those instances, as here, there is an increase in unmeasured organic acids.

Carbohydrate metabolism was undoubtedly altered in these nondiabetic patients despite the normal fasting blood sugars, since cortisone has been shown to decrease sensitivity to insulin.[5]

The very low sodium, high potassium intake must have contributed to the safety of the regimen, since there are abundant data reporting edema in patients receiving cortisone without restriction of their sodium intake.* In addition it has been possible to demonstrate negative potassium balances in subjects receiving large amounts of sodium per day, while retention of potassium occurred when sodium was stringently limited.[11] It seems wise to recommend rigid, perhaps even complete, sodium restriction in patients with edema or a tendency to edema because of congestive heart failure or low serum albumin concentrations. With such a low intake the patients must be observed carefully for development of sodium depletion or water intoxication. If sodium losses occur either through the kidney or through extrarenal routes, it may be necessary to administer this cation. Extremely hot weather must also make one careful about the development of sodium depletion. Maintenance of normal sodium concentrations after therapy was instituted despite the marked sodium restriction attests to the ability of the kidneys to maintain homeostasis, especially since these patients did not become dehydrated or edematous.[1]

No problems involving potassium metabolism were recognized. Unpublished studies did not reveal negative balances of this cation. The hypochloremic alkalosis that appeared could not be related to negative cellular balances of potassium. It is worth mentioning that the diet administered to these patients might be hazardous to patients with renal failure because it contained 150 mEq. or more of potassium per day. Such patients may not handle this large amount safely, although it is desirable to give large amounts of potassium whenever cortisone is administered. The high potassium intake may also permit some leniency in the sodium ration,[12] but our data do not permit us to comment on this problem.

The frequency of isolation of β hemolytic streptococci from the nasopharynx of these children makes us question the adequacy of our prophylaxis even though no clinical sequelae were noted. It is likely that cortisone had reduced the person's ability to ward off infections as well as localize them and that larger amounts of penicillin are needed. Experimental data indicate depression of the reticuloendothelial system in animals receiving cortisone.† Heller has demonstrated that the addition of vitamin B_{12} and choline to similar therapy in mice will reverse this decrease in responsiveness to antibiotics.[13] Ingle has shown the increased risk of infection to rats given large doses of cortisone (17-66 mg. per kilogram of body weight per day).[15] Jawetz has reported increased susceptibility to bacterial infection in mice receiving smaller doses of cortisone, 8 to 10 mg. per kilogram of body weight per day.[16] Even though the patients received only 100,000 units buffered oral penicillin between meals, none developed recognized β hemolytic streptococcal infections when not receiving cortisone. Breese and collaborators have suggested 400,000 to 500,000 units of penicillin a day as prophylaxis in the absence of cortisone.[17]

Antistreptolysin O titers in the children treated here fell much more rapidly than those reported by Diehl and co-workers. The 19 patients with rheumatic fever who had antistreptolysin O titers 500 units or greater per milliliter of serum, to whom Diehl gave intramuscular benzathine penicillin prophylactically, took 1 to 11 months for these values to return to normal. One-half of them only were normal at seven months.[18] If the

* References 5-10.

† References 13 and 14.

benzathine penicillin did not retard the rate of decline of this antibody, then our regimen accelerated its fall. The latter explanation seems more likely.

The data presented in this paper do not enable one to predict which patients will show activity of rheumatic fever when treatment is discontinued. It seems reasonable to suggest, however, that the patient is not well if any of the indices of inflammation are abnormal. The reverse does not seem true while cortisone is administered.

The relatively rapid return to normal of the indices of inflammation also suggests the important suppressive action of cortisone on rheumatic fever. Recurring abnormalities when therapy is prematurely discontinued together with a subsequent return to normal after retreatment lend weight to this concept. Those patients who do poorly do not show similar favorable changes.

SUMMARY

A regimen supplying cortisone in large amounts, marked sodium restriction, and a high potassium intake plus penicillin, supplementary vitamins, and iron to children with active rheumatic carditis was well tolerated with mild hypochloremic alkalosis as the only abnormality. The marked sodium restriction means that patients must be observed carefully for development of hyponatremia, but this was no hazard in these children.

Miss Mary Shuman and Dr. Aaron Stock aided in cultures and forwarding of serum to Miss Edythe Rose who performed the majority of antistreptolysin O titers at the National Institutes of Health.

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Hydralazine in Nephritic and Normal Children with Renal Hemodynamic Studies

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INTRODUCTION

During recent years several therapeutic agents have been made available for use in the control of hypertension. One of these, hydralazine (Apresoline), has been widely used in adults. Because of the reported dual capacity of reducing blood pressure and at the same time increasing the renal blood flow in patients with hypertensive disorders,* hydralazine appeared to be an ideal agent in the management of hypertension associated with acute glomerulonephritis. For this reason the following study was undertaken to evaluate the clinical usefulness of this drug and its influence on renal hemodynamics in normal children and in children during the hypertensive phase of acute and chronic nephritis.

These studies were being conducted at the same time that McCrory and Rapoport [4] were investigating this agent. They have reported the effects of hydralazine on blood pressure and renal function in seven children with acute nephritis, two of whom were in the hypertensive phase of the disease. These authors report a significant temporary depression of glomerular filtration rate and urine flow. The renal plasma flow was irregularly increased or decreased; the filtration fraction was uniformly decreased.

John and Mary R. Markle Scholar (Dr. Tuttle).

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From the Division of Pediatrics, University of Tennessee College of Medicine, John Gaston Hospital, and the Le Bonheur Children's Hospital.

* References 1-3.

METHODS AND MATERIALS

Details of our clinical observations will be mentioned in the discussion of results which follows.

Ten children between the ages of 4 and 11 years admitted to the John Gaston Children's Hospital from January, 1952, to April, 1954, for elective surgical procedures constituted the normotensive group.

Twenty-four patients with acute nephritis and hypertension (73% of admissions with acute nephritis) and 2 patients with chronic nephritis and hypertension admitted to the hospital from November, 1951, to October, 1953, are included in this report. Gross and/or microscopic hematuria, albuminuria, oliguria, and edema in addition to hypertension of 140/90 or greater was present in these cases (Table 1). The high incidence of hypertension in this series is attributed to the low socioeconomic status of these patients in whom the disease was permitted to advance to a state beyond that usually seen in acute nephritis before medical assistance is sought.

The glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and urine flow (UF) were determined on the normal children, on nine of the acute nephritis patients with hypertension, and on two patients with chronic nephritis who had hypertension. Renal clearance studies were not performed on the remainder of the hypertensive acute nephritic patients on whom clinical observations are reported (Table 1) because of impending or frank cardiac failure and serious oliguria and anuria. The GFR was determined by the clearance of mannitol and ERPF by the clearance of paraaminohippurate, using standard clearance techniques. All clearance values were corrected to 1.73 square meters of surface area. Utilizing the GFR and ERPF, the filtration fraction (FFr), $\frac{GFR \times 100}{ERPF}$, effective renal blood flow (ERBF), $\frac{ERPF}{1-Hct.}$, and the "crude" renal vascular resistance (RVR), $\frac{\text{Mean blood pressure}}{ERBF}$, were computed.

Two control periods of 15 minutes each were carried out before administering hydralazine. Blood

TABLE 1.—*Clinical Data Prior to Hydralazine Therapy*

Patient	Age, Yr.	Sex	Duration of Present Illness, Days	BP, Mm./Hg	Urinary Findings: Albuminuria	Urinary Findings: RBC/HPF.	Urinary Findings: N.P.N., Mg./100 Cc.	Additional Complications
Acute Nephritics								
R. J.	4	M	6	138/110	3+	40-60	28	.....
C. M.	10	F	2	170/140	0 †	0 †	44	Convulsions
E. L.	3	M	3	142/100	3+	Innum.	29	Early cardiac failure
C. H.	8	F	7	150/110	4+	30-40	35	Cardiac failure and convulsions
M. W.	3	F	5	150/102	3+	Rare	35	.....
A. H.	5	M	2	190/130	2+	12-20	33	Cardiac failure, convulsions and anuria (15 hr.)
G. E. C.	2	M	7	158/116	3+	10-15	25	.....
E. W.	6	M	8	150/86	3+	Rare	149	Comatose
G. C.	3	M	1	140/100	4+	6-12	38	.....
J. W.	10	M	21	198/150	2+	20-25	88	Cardiac failure
E. H.	2	M	7	165/125	1+	3-5	26	Early cardiac failure
J. F.	8	M	5	150/108	3+	Innum.	57	.....
J. R.	7	M	5	155/105	2+	4-5	44	Cardiac failure
L. N.	11	M	7	170/120	1+	7-8	35	.....
V. B.	11	F	7	156/110	1+	15-20	28	Convulsions
R. S.*	5	M	7	188/140	2+	Occ.	32	.....
R. P.*	13	M	2	175/100	2+	Innum.	26	Cardiac failure and convulsions
D. J.*	12	M	2	150/110	2+	7-9	25	.....
W. W.*	9	M	1	152/110	2+	Occ.	26	.....
I. B.*	7	F	1	170/120	4+	0-2	43	.....
J. H.*	7	M	7	160/120	1+	Rare	27	Cardiac failure
P. P.*	3	F	3	142/92	2+	20-25	57	.....
J. B.*	3	M	2	134/100	1+	10-30	59	.....
W. S.*	9	M	4	150/110	4+	10-12	96	.....
Chronic Nephritics								
D. M.*	9	M	?	178/120	3+	10-20	76	Convulsions
W. J.*	5	M	?	156/120	3+	15-25	42	.....

* Renal clearances.
† Developed microscopic hematuria and albuminuria during 3d week of illness.

pressure was recorded at frequent intervals during the control and subsequent periods. Following the control periods, hydralazine was given in variable dosages (Table 2) by the intramuscular route with one exception (WS), when it was given orally. The mannitol and paraaminohippurate were permitted to perfuse at a constant rate to assure maintenance of adequate and constant levels while the patient was being observed for impending hypotensive effects following administration of the drug. When this effect was achieved, two or three successive 13- to 25-minute periods were run. For the most part the clearances terminated at approximately 1 hour and not more than 1 hour and 50 minutes following the administration of hydralazine. The hypotensive effect appeared within 15 to 30 minutes after administration of the drug.

The patients were considered to be in a state of hypertension when the blood pressure was 140/90 or higher following a preliminary period of bed rest and sedation with phenobarbital. In patients with encephalopathy and/or cardiac failure on whom clearances were not performed, the drug was started earlier, and in a few instances 100 mg/kg. of magnesium sulfate in single doses or repeated in four hours was administered prior to the use of hydralazine.

RESULTS

Clinical Observations.—Twenty-four patients with acute glomerulonephritis and two with chronic nephritis complicated by hypertension were observed following the use of hydralazine. Pertinent clinical data, including age, sex, duration of illness, blood pressure, urinary findings, N. P. N. levels, and incidence of severe complications prior to hydralazine therapy are shown in Table 1. The erythrocyte sedimentation rate was accelerated in 85% of the cases. Ten patients received the drug intramuscularly, 7 orally, and 9 patients received it by both routes.

These patients were observed in order to determine (1) effective dosage, (2) the time for onset, duration, and degree of hypotensive response, (3) the influence of hydralazine therapy on the clinical course and final outcome of the patient, and (4) untoward side effects. Special attention was directed toward evaluating the usefulness of hydralazine in the management of the severe com-

TABLE 2.—*The Effect of Hydralazine on Renal Function and Mean Blood Pressure in Normal and Nephritic Children**

Date of Clearance	Patient	Age, Yr.	Sex	Dosage, Mg/Kg. I. M.	GFR †		ERPF †		FFr †		ERBF †		MBP †		RVR †		UV †	
					I	II	I	II	I	II	I	II	I	II	I	II	I	II
Normal Children																		
11/13/52	R. L.	4	M	0.26	153	122	641	537	23.8	22.7	...	...	86	76	.....	.....	1.95	2.64
2/ 8/52	N. E.	9	M	1.17	153	103	521	660	29.4	15.6	733	930	95	76	0.130	0.082	6.80	0.54
1/28/52	M. C.	6	F	1.13	147	140	542	915	27.1	15.6	753	1308	98	72	0.107	0.079	3.70	0.61
4/14/54	J. C.	10	M	1.00	147	133	685	720	24.4	18.5	1145	1200	90	70	0.078	0.059	4.44	0.62
2/ 6/52	J. F.	10	F	0.86	144	87	613	642	23.6	13.8	914	957	97	75	0.130	0.055	3.00	0.56
4/19/54	R. J.	11	F	0.50	138	126	590	795	23.4	15.9	955	1285	98	78	0.102	0.061	7.49	1.35
4/20/54	B. B.	7	M	0.56	137	150	520	855	26.4	17.6	835	1370	78	72	0.093	0.052	4.20	2.05
2/ 1/52	F. M.	9	M	0.80	129	84	556	690	23.2	12.1	848	1054	84	66	0.099	0.063	3.60	0.68
1/31/52	R. B.	11	F	0.78	102	89	500	513	20.3	17.5	795	820	101	69	0.126	0.084	4.50	0.84
11/11/52	T. C.	9	F	0.25	97	77	435	326	22.3	23.6	...	...	89	83	.....	.....	3.14	2.06
	Mean values.....				135	111	560	665	24.4	17.3	872	1116	92	74	0.108	0.067	4.28	1.20
Acute Nephritis with Hypertension																		
10/27/53	R. S.	5	M	1.09	168	120	550	503	30.5	23.8	1018	931	120	85	0.118	0.091	4.52	0.52
1/19/53	R. P.	13	M	1.04	145	136	850	824	17.1	16.5	1519	1471	130	120	0.084	0.082	8.85	6.87
4/14/53	D. J.	12	M	1.09	136	49	724	460	18.9	10.9	1114	708	147	91	0.134	0.152	1.71	0.92
4/22/52	W. W.	9	M	0.90	123	86	685	667	18.0	13.2	1038	1012	147	117	0.142	0.119	0.63	0.51
4/19/52	I. B.	7	F	0.34	96	12	753	142	12.8	8.9	1175	222	119	94	0.102	0.448	2.29	....
5/22/53	J. H.	8	M	0.83	94	92	366	555	25.6	16.5	531	804	119	107	0.223	0.132	3.37	1.10
3/ 5/52	P. P.	3	F	0.61	58	30	328	265	17.6	11.1	469	379	117	95	0.249	0.250	3.20	1.45
10/30/52	J. B.	3	M	0.25	51	32	516	405	9.9	8.8	747	586	101	91	0.136	0.157	0.78	0.51
3/14/52	W. S. (No. 1)	9	M	0.93	39	5	549	132	6.9	4.2	785	189	124	73	0.158	0.398	1.08	0.07
3/17/52	(No. 2)	..	..	0.93‡	38	36	617	605	6.3	5.9	881	864	133	120	0.149	0.138	1.09	1.09
	Mean values.....				95	60	594	456	16.4	12.0	928	717	126	99	0.150	0.197	2.75	1.45
Chronic Nephritis with Hypertension																		
10/23/53	D. M.	9	M	0.72	11	3	47	33	23.1	9.3	66	47	137	95	2.060	2.060	1.40	0.52
8/ 8/53	W. J.	5	M	0.28	10	7	66	61	15.2	11.0	106	99	120	115	1.180	1.170	3.56	3.10

* All values corrected to 1.73 sq. m. surface area.

† I indicates control periods, average; II indicates average of clearance values at time of maximum blood pressure response; GFR, cc/min.; ERPF, cc/min.; FFr, GFR × 100/ERPF; ERBF, ERPF/1 — HCT — cc/min.; MBP, mm/Hg; RVR, MBP/ERBF; UV, cc/min.

‡ Orally administered hydralazine.

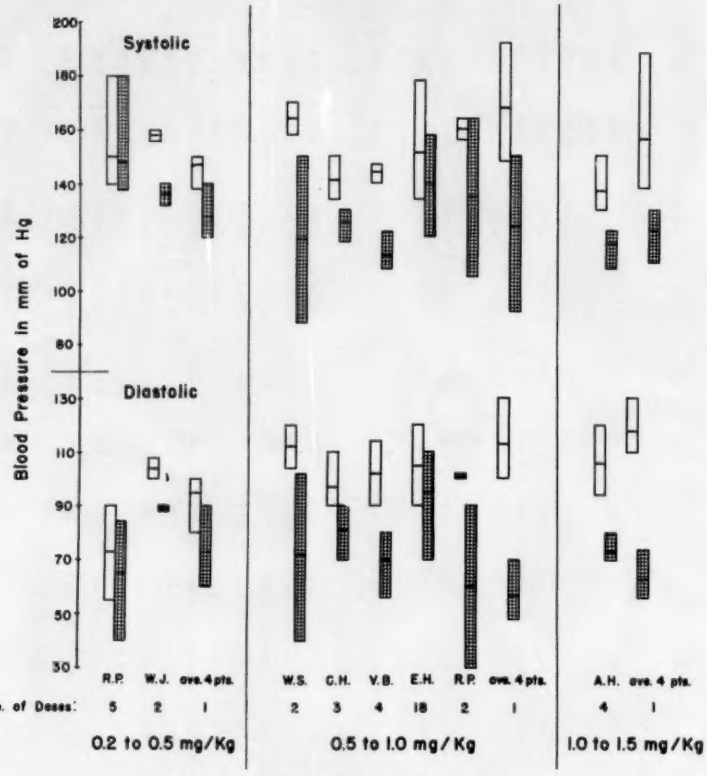

Fig. 1.—Range and average systolic and diastolic blood pressure prior to and following intramuscular administration of hydralazine. Open bars indicate control period; cross hatched bars, after hydralazine; heavy line, average value.

plications, i. e., encephalopathy and cardiac failure, secondary to the hypertension.

Dosage: The dosage ranged from 0.2 to 1.5 mg/kg. body weight intramuscularly, and from 0.5 to 2.5 mg/kg. orally. Frequency of administration was governed by duration of the therapeutic response but was never repeated sooner than 90 minutes following a previous dose. In a 24-hour period it was seldom necessary to administer more than six effective doses, and frequently a single dose was sufficient.

Figure 1 illustrates the range and average systolic and diastolic blood pressures prior to and following various dosages of hydralazine when administered intramuscularly. Significant reductions in blood pressure were uniformly obtained in all patients receiving more than 0.5 mg/kg. intramuscularly. Patients receiving less than 0.5 mg/kg. (0.2 to 0.5 mg/kg.) usually responded, but not uniformly. Doses in excess of 1 mg/kg. were usually no more effective than doses 0.5 to 1 mg/kg.

Figure 2 similarly illustrates the response obtained from various dosages of orally administered hydralazine. Because of the observations following the intramuscular use, mentioned above, the smallest dose used was 0.5 mg/kg. This figure shows that 0.5 to 1 mg/kg. is the optimal dosage, and no advantage was obtained by using doses up to 2.5 mg/kg. When indicated in the presence of serious complications, i. e., cardiac failure and encephalopathy, we therefore recommend that doses of 0.5 mg/kg. be used initially and that subsequent doses not exceed 1 mg/kg. by either route of administration. The intramuscular route was preferred during the early phase of therapy and when there was a history of vomiting.

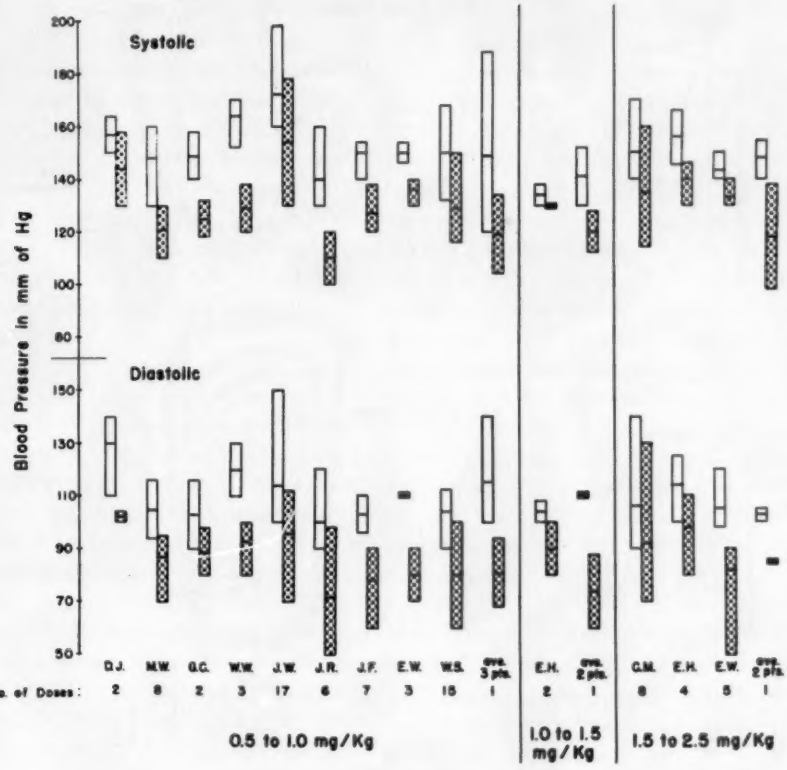

Fig. 2.—Range and average systolic and diastolic blood pressure prior to and following oral administration of hydralazine. Open bars indicate control period; cross hatched bars, after hydrazaline; heavy line, average value.

Response: In this series a blood pressure of 140/90 mm. Hg or higher constituted a state of hypertension of sufficient degree to require hypotensive therapy. Therefore, a fall in blood pressure below this level after a dose of hydralazine was considered to constitute a good therapeutic response. Typical blood pressure responses to effective doses in two patients following the oral and intramuscular administrations, respectively, are illustrated in Figure 3. Following the intramuscular injection of hydralazine, the time for onset of a hypotensive response ranged from 5 to 20 minutes. The mean time required for maximum hypotensive response was 40 minutes, with a range from 15 to 150 minutes. When the drug was administered orally, the onset of response was noted usually within 20 to 45 minutes; a few cases required as long as 1 hour before a response was observed. The time required for maximum hypotensive response was more unpredictable when the drug was administered orally than after the intramuscular injection, the average being 113 minutes, with a range from 15 to 210 minutes.

The length of time that the blood pressure remained below 140/90 was considered as the duration of therapeutic response. Four patients, J. W., E. H., C. M., and A. C., with rather severe hypertension before hydralazine therapy did not satisfy the above criteria for a good therapeutic response but experienced a definite fall of both systolic and diastolic pressures following the use of hydralazine. On the other hand, seven patients, J. H., P. P., W. J., J. B., E. L., L. N., and G. C., remained normotensive after receiving one dose of hydralazine. The average duration of therapeutic response in the

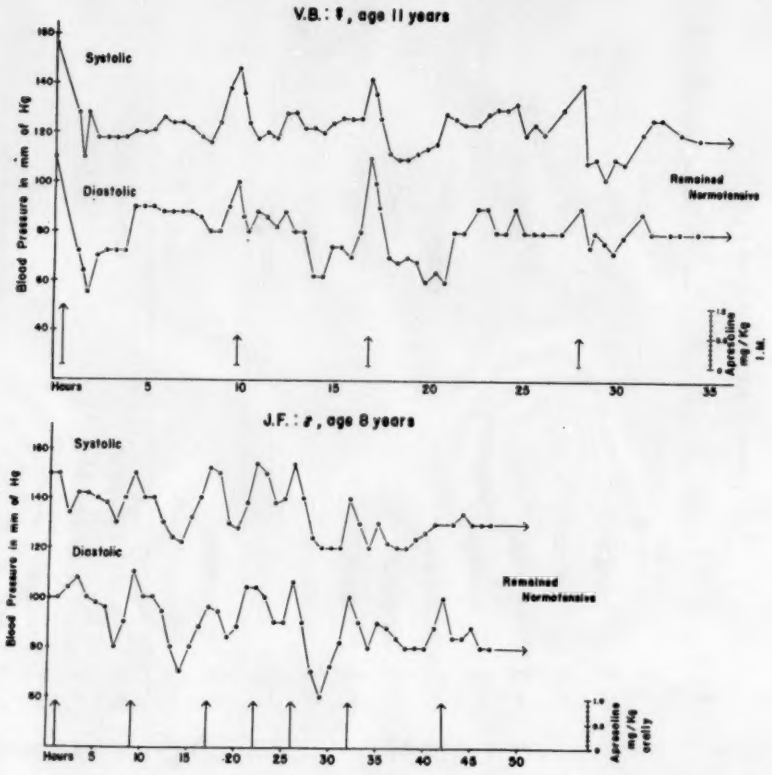

Fig. 3.—Typical hypotensive responses following intramuscular and oral administration of hydralazine in children during the hypertensive phase of acute nephritis.

remaining 14 patients was 7.5 hours following intramuscular or oral administration. It was frequently observed, Figures 1 and 2, that the reduction in diastolic blood pressure was greater than the reduction in systolic pressure. This observation has been made previously by Fries and co-workers.[5] They attributed this to an increased cardiac output along with a marked decrease in total peripheral resistance resulting in greater decrease in diastolic than systolic pressure.

The need for continuous hypotensive therapy in these patients ranged from 1 to 11 days, with an average of 3.5 days. This compares favorably with results obtained in a series of patients treated with magnesium sulfate alone.†

Hydralazine, through its consistent hypotensive effect, has proved to be a very valuable drug in the management of severe complications, such as encephalopathy and cardiac failure associated with acute glomerulonephritis. In such patients where magnesium sulfate has been ineffective, we wish to recommend the use of hydralazine in spite of adverse depression of renal functions to be discussed below. Patients with these complications are listed in Table 1. Twenty-seven per cent of the patients had encephalopathy which was readily controlled with hydralazine and barbiturates. In no instance did signs of encephalopathy recur following institution of hydralazine therapy. V. B., Table 1, Figures 1 and 3, illustrates a case of hypertensive encephalopathy which was previously diagnosed elsewhere as a brain tumor. Magnesium sulfate had been ineffective, and hydralazine, in doses of 0.6 and 1.2 mg/kg. at 8- to 10-hour intervals, readily controlled the blood pressure and resulted in a cessation of convulsions with complete

† Unpublished data.

recovery. Thirty per cent, or eight patients, had early or advanced cardiac failure, and digitalization in addition to hydralazine was required in four of them. In the remaining four patients this drug alone was effective in combating cardiac failure. In one patient, A. H. (Table 1, Fig. 1), who was anuric for two days and had severe hypertension with cardiac failure and encephalopathy, hydralazine was used to control the hypertension, and this patient also made a complete recovery.

It is of interest that two patients, E. L. and R. P. (Table 1, Fig. 1), similar to V. B. above, with cardiac failure or encephalopathy also received the generally recommended dose of 100 mg/kg. of magnesium sulfate (0.2 cc. 50% solution/kg.) intramuscularly twice within four hours without effect prior to hydralazine therapy. Following a single dose of 0.5 mg/kg. of hydralazine intramuscularly, E. L. responded well and remained normotensive thereafter; R. P. also responded well to intramuscular hydralazine in doses of 0.4 and 1 mg/kg. but did not respond to doses of 0.2 mg/kg. As mentioned above, in no case was there failure to obtain a hypotensive response to an initial dose of 0.5 mg/kg. or greater.

Although Fries [5] observed that hydralazine increased cardiac output above the physiologic range for resting subjects, in no instance in our series was cardiac failure precipitated by hydralazine therapy.

Influence of Hydralazine on the Clinical Course and Final Outcome of the Patients: The clinical course and final outcome of the patients in this series were similar to that of patients with acute glomerulonephritis treated with magnesium sulfate and/or barbiturates.‡ Early in the course of the disease the patients usually became normotensive and were maintained in that state with relative ease.

Although renal function may be further depressed immediately following the use of hydralazine in those acute nephritic patients with a normal or elevated N. P. N. prior to hydralazine therapy, no significant increase was observed following its use. Findings upon serial urinalyses during the period of hospitalization were similar to those of patients not receiving hydralazine. Erythrocyte sedimentation rates were similar to those of other patients with acute glomerulonephritis and gradually returned to normal within 60 days of the onset of the illness. Follow-up observations in the outpatient clinic of the patients who had received hydralazine therapy revealed that chronic glomerulonephritis had not developed in any instance and that the general course of the disease had not been adversely influenced. It was impossible to distinguish hydralazine-treated patients from those in whom the hypertension was treated by other forms of therapy. One patient, G. E. C., Table 1, six months after the onset of his illness has had a persistent microscopic hematuria and slight albuminuria. No deaths occurred, regardless of therapy, during the period of these observations.

Untoward Side-Effects: In our experience, untoward side-effects due to hydralazine were rare and were of no serious consequence when they did occur. The most unpleasant side-effect noted was postural hypotension with mild nausea and faintness which occurred chiefly among uncooperative patients. This side-effect was largely eliminated by making special efforts to keep the patient in a recumbent position until he had adjusted to the relative hypotension. The patients occasionally complained of nausea following both oral and intramuscular administration, but vomiting was rare. Moderate tachycardia was frequent and caused no alarming symptoms. None of the patients complained of palpitation, headache, anginal pain, or numbness and tingling of the extremities. Signs of toxicity, such as urticaria and drug fever, were not observed. The patients in this series did not require hypotensive therapy for a sufficient period of time to develop the late undesirable effects of hydralazine, such as anemia and the arthritis-like syndrome.

Only two patients, J. W. and E. W. (Fig. 2), developed a definite resistance to the

‡ Unpublished data.

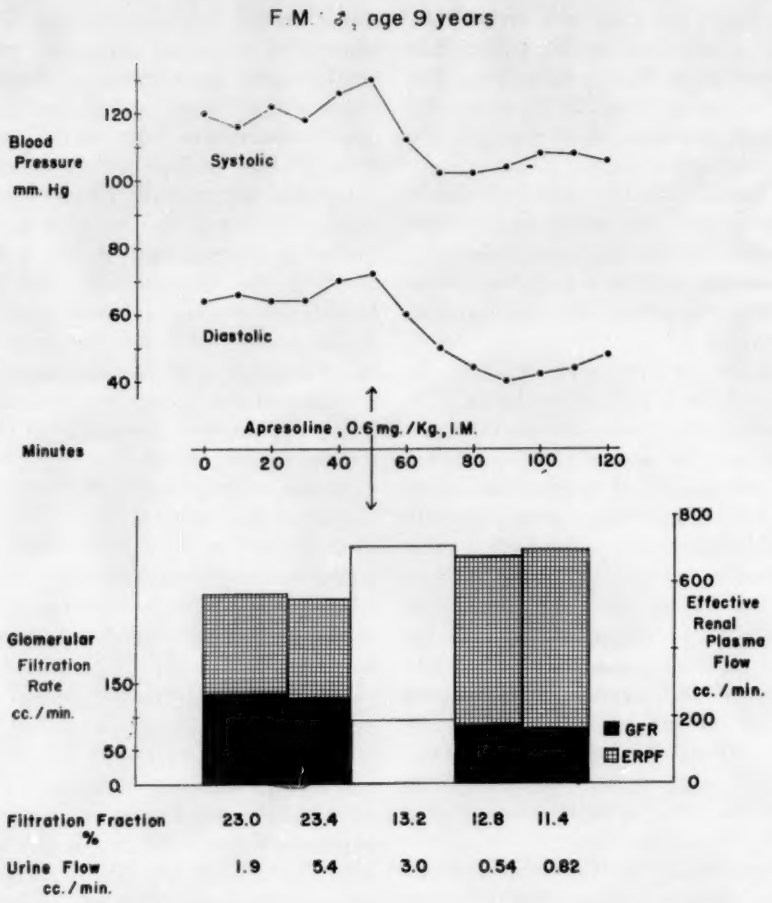

Fig. 4.—Typical blood pressure response and renal functions after hydralazine in a normal child.

hypotensive effect of the drug. In both instances the hypertension was severe and of longer duration than is usually observed. J. W. became resistant after 14 doses during eight days of therapy, and E. W. after 9 administrations during five days of therapy. E. W. also became resistant to the hypotensive effect of intramuscular magnesium sulfate. Without further therapy this patient gradually became normotensive and at the time of this writing apparently is well.

Influence of Hydralazine on Renal Hemodynamics.—A. Normal Children: Early in this study normal children were studied in order to determine the possible effective dose and influence of hydralazine upon renal hemodynamics before attempting extensive use on hypertensive patients with acute nephritis. Furthermore, it was felt information concerning the influence on renal hemodynamics in normal children would be of value in appraising the use of this drug during the management of hypertension attributable to nonrenal causes.

Data for normal and nephritic children prior to and following hydralazine therapy are given in Table 2. Summarizing and statistical data are given in Table 3. Renal clearance values for normal children include 15 children previously reported.[6] Figure 4 correlates blood pressure response and influence on renal function in a normotensive child following hydralazine administration.

The mean blood pressure (MBP=diastolic pressure+⅓ pulse pressure) prior to the administration of the drug ranged from 78 to 101 mm. Hg, with a mean of 92 mm. Following hydralazine, the range in MBP was 66 to 83 mm. Hg, with a mean of 74 mm. Hg. This represents a highly significant reduction (critical ratio of 6.43).

Glomerular filtration rate (GFR) in normal children prior to the administration of hydralazine ranged between 97 and 153 cc/min., with a mean of 135 cc/min. (Table 3). Hydralazine resulted in a statistically significant decrease in the GFR (critical ratio 4.28), with a range of 77 to 150 cc/min. and a mean of 111 cc/min. A slight increase occurred in only one child (B. B.).

The effective renal plasma flow (ERPF) during the control period ranged from 435 to 685 cc/min., with a mean of 560 cc/min. Following hydralazine, the ERPF ranged from 326 to 915 cc/min., with a mean of 665 cc/min., and represented a significant increase in this function (critical ratio of 3.57). The plasma flow was decreased by the drug in only two children (T. C. and R. L.). These two children received relatively small doses of 0.25 and 0.26 mg. per kilogram, respectively. T. C. was in the lower limits of normal during the control period. As would be anticipated, the effective renal blood flow (ERBF) was likewise significantly increased, with a critical ratio of 3.03. The decrease in renal vascular resistance to be discussed below and a probable increase in cardiac output as observed in adults [5] serve to explain these changes in plasma and blood flow.

The filtration fraction (FFr) was significantly decreased as a result of these changes in GFR and ERPF. Before hydralazine, the FFr ranged from 20.3 to 29.4%, with a mean of 24.4% compared with a range of 12.1 to 23.6% and a mean of 17.3% after hydralazine.

The crude renal vascular resistance (MBP/ERBF), as would be expected with a fall in blood pressure and an increased blood flow, was significantly reduced (critical ratio of 6.62) by hydralazine. The range before administration of the drug was 0.078 to 0.130, with a mean of 0.108. Following the drug, the RVR ranged from 0.052 to 0.084, with a mean of 0.067. It appears from these observations that efferent arterioles in normal children are disproportionately more dilated than the afferent arterioles.

The end-result of these alterations is a marked reduction in urinary output (Table 2). We cannot state the duration of the influence on renal functions in these normal children; however, from our observations on patients with nephritis, we believe it is transitory.

TABLE 3.—*Summarizing Data on Normal and Hypertensive Children with Nephritis*

Group	No. Pts.		GFR, Cc./Min.	ERPF, Cc./Min.	ERBF, Cc./Min.	GFR × 100 / ERBF	MBP, Mm./Hg	RVR, MBP/ERBF
Normal before hydralazine.....	10	Range	97-153	435-685	733-1,145	20.3-29.4	78-101	0.078-0.130
		Mean	135	560	872	24.4	92	0.108
Normal after hydralazine.....	10	Range	77-150	326-915	820-1,370	12.1-23.6	66-83	0.052-0.084
		Mean	111	665	1,116	17.3	74	0.067
Critical ratio	..	.....	4.28	3.57	3.03	4.94	6.43	6.62
Normals	25 *	Range	97-175	435-784	600-1,145	17.7-29.4	78-101	0.078-0.130
		Mean	132	599	885	22.7	92	0.108
Critical ratio *	..	.....	2.97	0.104	0.52	3.37	6.77	2.21
Nephritics before hydralazine...	10	Range	38-168	328-850	469-1,519	6.3-30.5	101-147	0.084-0.249
		Mean	95	594	928	16.4	126	0.150
Nephritics after hydralazine....	10	Range	5-136	132-824	189-1,471	4.2-23.8	73-120	0.082-0.448
		Mean	60	456	717	12.0	99	0.197
Critical ratio	..	.....	3.43	2.63	2.61	4.61	4.7	2.0

* Critical ratio for GFR, ERPF, ERBF, and FFr derived from data obtained from 10 nephritic patients of present series and 25 normal children, 15 of whom were previously reported.[6] The critical ratio for the MBP and RVR was derived from data during this study.

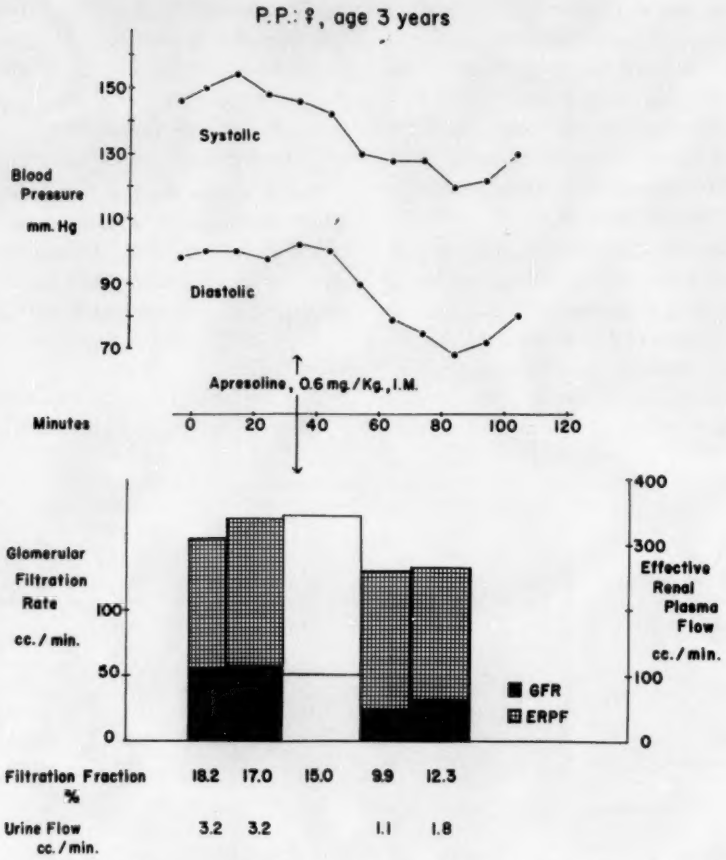

Fig. 5.—Typical blood pressure response and renal functions following hydralazine in a child during the hypertensive phase of acute nephritis.

B. Children with Acute Nephritis: Reference to Tables 2 and 3 reveals that the GFR and FFr were significantly reduced as a result of acut nephritis; however, in isolated cases these functions were within normal limits. Statistical analysis failed to show that the ERPF and ERBF were significantly altered in these nephritis patients. Subnormal values were obtained in J. H. and P. P., and in the remainder of patients they were normal or supranormal. These findings confirm the observations of Earle and coworkers,[7] who state "that the reduced filtration fraction observed in acute glomerulonephritis represents a greater barrier to glomerular filtration than to the passage of blood through the glomerular apparatus." The MBP in these patients before treatment ranged from 101 to 147 mm. Hg, with an average of 126 mm. Hg, and represented a highly significant increase over normal children. The RVR showed a definite tendency to be increased prior to therapy and approached statistical significance with a critical ratio of 2.2.

Figure 5 graphically represents the usual effects of hydralazine on blood pressure and renal functions in patients with acute nephritis. There was a uniform and a highly significant decrease in MBP in these patients as a result of the drug. Following the drug, the MBP ranged from 73 to 120 mm. Hg, with a mean of 99 mm. Hg (Table 3).

Hydralazine therapy, Table 3, caused a significant decrease in the already reduced GFR and may be explained as a result of

the hypotensive response and efferent arteriolar dilation with a reduction in the filtration pressure. The range prior to therapy was 38 to 168 cc/min., with a mean of 95 cc/min. After therapy the GFR ranged from 5 to 136 cc/min., with a mean of 60 cc/min.

In contrast to the influence of hydralazine on normal children, we observed a statistically significant decrease in ERPF and ERBF following therapy. The ERPF and ERBF averaged 594 and 928 cc/min., respectively, before hydralazine and 456 and 717 cc/min. after hydralazine. In only one of the patients (J. H.) was there an increase in ERPF and ERBF. These observations are unlike those reported in studies on adults with hypertension from various causes.§ If hydralazine causes an increase in cardiac output as has been observed in hypertensive patients,[5] one might state that the kidneys did not participate in vasodilatation to the same degree as other vascular areas of the body.

The filtration fraction was significantly reduced from the mean of 16.4% to 12.0% by hydralazine. This reduction is attributed to a disproportionately greater decrease in GFR than ERPF and not associated with an actual increase in ERPF along with a decrease in GFR, as occurred in normal children. The urinary output was consistently reduced by hydralazine.

In this group of nephritic patients, hydralazine resulted in an insignificant change in the mean "crude" RVR. There was marked increase in I. B. and W. S. (No. 1). In three out of four patients in whom hydralazine caused a decrease in RVR, it was attributed to a disproportionately greater decrease in MBP than ERBF; in the fourth patient (J. H.) it was attributed to an absolute increase in ERBF. In two patients there was no change in RVR.

There were four hypertensive children (R. S., R. P., D. J., and W. W.) who prior to treatment had normal GFR, ERPF, ERBF, and FFr. In D. J. and W. W. there occurred marked reductions in GFR and FFr following hydralazine, and in R. S. and R. P. there occurred only a slight decrease in these functions, which remained within the limits of normal. It is of interest that the ERPF and ERBF in all four of the patients was not depressed below the lower limits for normal children. The dosage administered to these children ranged from 0.9 to 1.09 mg/kg. I. M., which is to be considered a maximal effective dose. These observations serve to illustrate the unpredictable state of renal functions in hypertensive acute nephritic patients and that hydralazine in some cases does not cause a significant depression of renal function.

In addition to the clinical observations discussed above, which indicate that no permanent damage resulted from the use of hydralazine in the control of hypertension, we have follow-up clearance studies on patients treated with hydralazine, which indicate the transitory nature of the depression of renal function. W. S. (Table 2) had a marked reduction of MBP and all measured renal functions following hydralazine. Repeated doses of the drug were required to control the hypertension during the subsequent three days, at which time a renal clearance was performed. Reference to Table 2 reveals that the renal hemodynamics had returned to the pretreatment level. Thirty-six days later, after a period of several days of normotension, renal functions had returned to normal, with the exception of a slight decrease in GFR. R. S. and W. W., when studied 4 and 13 days, respectively, following the initial studies, had normal clearance values. In addition three of the patients included in the clinical observations (R. J., A. H., and C. M.) who did not have clearances before therapy had normal functions when studied on the 13th, 20th, and 42d days of their illness, respectively. Furthermore, the time for return of normal renal function in hydralazine-treated patients is comparable to that observed in 16 patients not treated with hydralazine.‖

C. Children with Chronic Nephritis: Two children, D. M. and W. J., were chronic

§ References 1-3.

‖ Unpublished data.

nephritic patients with acute hypertensive exacerbations of the disease. Both had severely depressed renal functions. D. M. was given 0.72 mg. of hydralazine per kilogram I. M. and had a further depression of all functions during the first 60 minutes, but by 110 minutes the ERPF and ERBF had returned to the control levels, with a persistent reduction in blood pressure. W. J. received only 0.28 mg/kg. I. M., with a slight decrease in MBP and without a significant alteration in renal function. Both of these patients received several doses of hydralazine subsequently without the appearance of oliguria or a progressive azotemia.

COMMENT

These results indicate a definite beneficial effect of hydralazine in the management of hypertension in acute nephritis. The benefits derived in the presence of serious complications, such as cardiac failure and enephalopathy, are outstanding and in our opinion justify its use in spite of temporary depression of renal function. The final outcome of all patients in this series was not unlike those treated with magnesium sulfate, and the therapeutic response was more predictable; however, until further observations are made, we feel that the use of this drug should be limited to the severe complications or when the use of magnesium sulfate has been unsuccessful in managing the hypertension.

SUMMARY

The hypotensive response and influence of hydralazine on renal hemodynamics has been studied in normal children and in children during the hypertensive phase of acute and chronic nephritis.

In normal children the GFR was depressed and the ERPF increased, with a decrease in the filtration fraction and urinary output.

In children with nephritis, the preexisting depression of GFR was temporarily exaggerated by hydralazine, and the ERPF was decreased during the period of hypotension following hydralazine. The filtration fraction and urinary output were decreased.

Hydralazine caused a decrease in the crude renal vascular resistance of normal children. In nephritis the crude renal vascular resistance was generally increased, and hydralazine caused no significant change.

The depression of renal functions by hydralazine was temporary, and the course of disease did not appear to be adversely influenced by the drug.

The use of hydralazine is recommended especially in the management of the severe complications, such as cardiac failure and encephalopathy, and may be effective in controlling the hypertension when magnesium sulfate in doses of 100 mg/kg. I. M. is ineffective; more widespread use awaits further observations.

The dosage schedule for hydralazine is outlined.

Elizabeth Stevenson and Thelma Howard gave technical assistance, and the nurses in the Children's Division of the John Gaston Hospital also cooperated in this study.

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Cytomegaly of the Adrenal Gland

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Cytomegaly, a unique and interesting morphologic change seen in the involutional human adrenal gland, was probably first introduced into the English medical literature by Kampmeier, in 1927. It has been further described by Craig and Landing, Potter, and Morrison.

It is the purpose of this paper to present certain observations on this entity gleaned from the autopsy material of the Children's Hospital from 1942 through 1953. During this period 1243 autopsies were performed. Fifty per cent of these autopsies were done on the bodies of infants 6 months of age or less. Eleven cases of adrenal cytomegaly were found.

METHODS

The protocols and tissue sections from 1243 autopsies were reviewed. The tissues were fixed in Zenker's solution, sectioned at 8μ from paraffin blocks, and stained with hematoxylin and eosin in the usual manner. In each case in which the adrenal gland sections revealed cytomegalic change, the clinical case records were examined and evaluated from the standpoints of history, physical examination, and clinical course.

REVIEW OF LITERATURE

An exhaustive review of the English literature concerning the human newborn adrenal gland was made. Only the above-mentioned articles were found which dealt with cytomegaly of the adrenal gland specifically, and in the many descriptions and discussions of the involutional phenomena noted in the human neonatal adrenal cortex, no hint that previous investigators had suspected a separate morphologic entity was found.

A recent article by C. Gasser reports "giant cells" in the adrenals of a group of premature infants who had suffered from hemolytic anemia in which Heinz bodies were found in the erythrocytes. No evaluation of this observation was given, however.

CHANGES NOTED IN THE ADRENAL GLAND AFTER BIRTH

At birth the human adrenal gland has a very thick cortex, of which 80% is fetal and 20% adult in type. At this stage the adrenal is one-third as large as the kidney; this fact is of interest from the standpoints of maturation, growth, and development, since the adult gland has a relatively thin cortex and is only one-thirteenth as large as the kidney.

During the first month of life, degenerative changes take place in the cortex which are apparently physiologic. This degeneration of the fetal cortex appears to be initiated by the birth processes and is unrelated to the gestational age of the infant. These changes, which reduce the adrenal cortex to near adult proportions, are not seen in the ordinary laboratory animals. Thomas, Kern, and Elliott and Armour independently in 1911, described the cortical involution, and papers of similar nature by Landau and Lewis and Pappenheimer followed four and five years later. All descriptions of the morphologic alterations are similar, and that of H. L. Jaffe is quoted below.

Degeneration is fully established at the end of the second week, and progresses rapidly thereafter, involving the cells of the inner cortical zones, which show extensive nuclear and protoplasmic destruction. The tissue is very vascular and there is some extravasation of blood. During the next five or six

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weeks, the debris is rapidly removed, leaving an intact thin glomerular layer. The deep cortex is replaced by lamellae of fibrous tissue with cell detritus in the meshes. At 6 months the fibrous replacement layer appears as a dense connective tissue zone, and the medulla has increased in size. During the succeeding months, the connective tissue layer becomes thinner, so that after the first year this fibrous zone remains only where two layers of cortex are adjacent. The thin intact glomerular layer collapses to form the convolutions of the adult cortex. According to Lewis and Pappenheimer, there is not an appreciable increase in the width of the cortex through regeneration up to the age of 3 years and the birth weight is regained only by the 12th year. Similar changes have been described in cortical accessory bodies and the process is considered a systemic one acting through the blood stream.

The degenerative changes in the cortex sometimes extend beyond the normal physiologic limits, leading to massive suprarenal hemorrhage in the newborn which is pathologic. The hemorrhage may completely destroy the medulla, converting the gland into a blood cyst. Rarely the cortex ruptures and blood extravasates into the peri-renal and retroperitoneal tissues.

Dr. M. C. Benner is in disagreement with Pappenheimer in that she believes that growth of the adult type cortex does take place before the age of 3 years.

The exact cause and significance of the involutional changes in the newborn adrenal cortex have to date not been demonstrated. A recent excellent and complete review by J. T. Lanman serves to reemphasize this and points out the lack of other real knowledge about the fetal and newborn adrenal cortex. Theories connecting the processes of involution with adrenal control of the other organs and tissues have been suggested, however (Marine, Lowe, Cipra).

SURVEY OF CLINICAL RECORDS

The clinical case records of the 11 cases of adrenal cytomegaly in the Children's Hospital material revealed approximately equal sex distribution. Six were females and five were males. All 11 cases were of the Caucasian race. The youngest was 3 hours and the oldest was 4 months of age. The average duration of life was found to be 19.5 days.

Nine of the 11 cases had anomalies but in only 5 were these anomalies clinically recognizable. Of the clinically recognizable anomalies, two were omphaloceles, and the remaining three were represented, respectively, by multicystic kidney, urethral anomalies, and polydactylism associated with diaphragmatic hernia. Table 1 represents a breakdown of the anomalies found and the organ systems involved in all nine cases. It will be noted that several cases had multiple anomalies.

Table 1.—*Congenital Anomalies Associated with Adrenal Cytomegaly*

Organ or System	No. Cases
Skin	1
Epidermolysis bullosa	
Skeletal	2
Polydactylism	
Hemihypertrophy	
Heart	2
Complex anomalies	
Urinary tract	2
Multicystic kidney	
Stricture of ureter	
Gastrointestinal tract	7
Macroglossia	
Omphalocele	
Fibrocystic disease of pancreas	
Hyperplasia of pancreatic islet tissue	
Meckel's diverticulum	
Miscellaneous	1
Diaphragmatic hernia	

Of the two patients not having anomalies, one had severe erythroblastosis fetalis due to Rh isoimmunization and the other had sepsis of the newborn complicated by kernicterus. It is interesting to note that in Craig and Landing's series, 11 of the reported 37 cases were associated with erythroblastosis fetalis.

Table 2.—*Adrenal Weights in Cases of Adrenal Cytomegaly*

Age, Days	Combined Adrenal Weight, Gm.
18	Not recorded
7/24	10.3
28	4.8
4	7.8
15	6.0
3 Premature infant	4.0
14	4.8
7	8.5
105	4.5
21	6.5
6	4.0

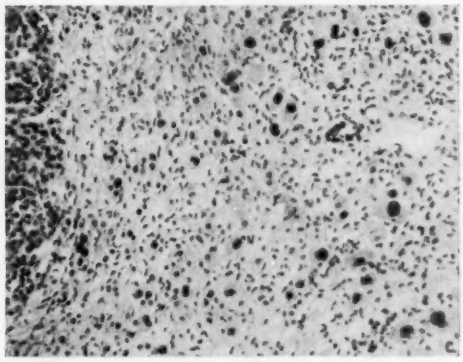


Fig. 1.—Cytomegaly of the fetal adrenal cortex (Mag. reduced approximately 0.3 from × 120).

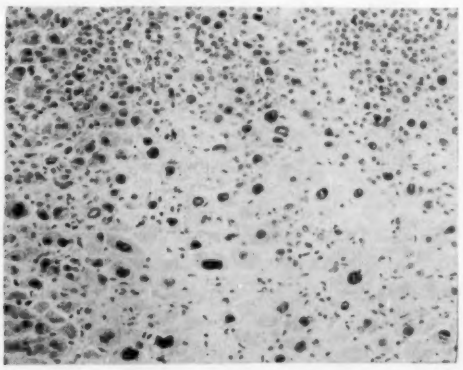
In 5 of the 11 cases, moderate to marked dehydration necessitating fluid therapy was noted, and 5 cases had severe vomiting, noninfectious diarrhea, or both.

PATHOLOGY

The combined weights of the adrenals having cytomegaly are shown in Table 2. These agree generally with the normal infant adrenal weights listed by Tähkä, the low weight for age occurring in a premature infant.

The gross appearance of the adrenals was not significant. Microscopically, the general architecture was preserved. In general, the normal ratio of adult to fetal cortex was maintained in accordance with age. One exception to this appeared in the areas severely involved by the cytomegalic phenomenon. Here, the fetal cortex appeared widened. As the term cytomegaly infers, abnormally large cells with an altered morphologic appearance were seen in the fetal cortex (Fig. 1, 2, and 3). Generally speaking, the cells occurred in groups, but single cells were seen. When in small numbers, they were found at the junction of the adult and provisional cortices, but when involvement was marked they extended throughout the width of the fetal cortex. None were seen in the adult cortex.

Fig. 2.—Cytomegaly of the fetal adrenal cortex (Mag. reduced approximately 0.3 from × 120).



In a single section, cytomegalic cells occurred in numbers from 10 to 1000+. The cell size range was from 20 to 100μ in the greatest diameter. The cytoplasm was pink and granular, and in many cells a more coarsely granular "inclusion" could be seen. The rim of cytoplasm about these inclusions was pink and hyaline. Intranuclear inclusions were not seen, but colorless vacuolar structures could be demonstrated in some of the nuclei (Fig. 3).

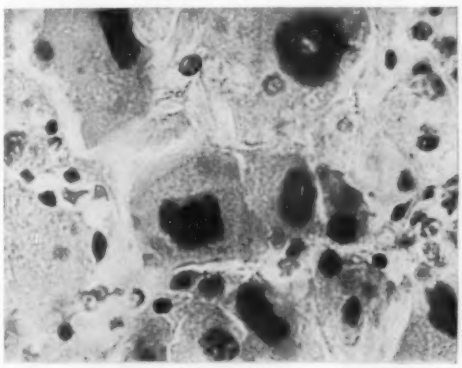


Fig. 3.—Cytomegaly of the fetal adrenal cortex showing cellular detail—note the nuclear vacuole, upper right (Mag. reduced approximately 0.3 from × 516).

The nuclei of the cytomegalic cells were generally hyperchromatic and enlarged two to three times. There was a moderate variation in size and shape and a marked variation in the cytoplasmic-nuclear ratio. The chromatin pattern was either smudged, coarse and blocked, or fine and rod-like. Rupture of the nuclei often occurred with spilling of the chromatin "rods" into the cytoplasm and matrix. Nucleoli were not prominent,

and mitotic activity was not seen in the cytomegalic cells.

Thorough study of the tissue sections failed to reveal cytomegaly or intracellular inclusions in any organ other than the adrenals.

COMMENT

The foregoing material in this paper reveals the fact that adrenal cytomegaly is a distinct entity concerning which little has been written. It also becomes obvious that specific knowledge of cause and effect relationships concerning the phenomenon is nil. At this stage in the development of the natural history of a morbid condition it is important to draw together any and all facts and observations concerning the entity for use in further investigation.

Of the tabulated material pertaining to our 11 cases, the most consistent and interesting dealt with the coexistent congenital anomalies. None of the previous investigators describing this change have been impressed by such relationship in their series of cases.* Nine of our 11 cases had coexistent anomalies, and in several, multiple anomalies were noted. It is interesting that the formation of all of these anomalies dated to the same period in embryologic life (fifth to seventh week). The association in our series (Table 1) of cytomegalic change with pancreatic fibrosis has not been reported previously. Gillman and Gillman, however, observed the association of "delayed" involution of the provisional adrenal cortex with the occurrence of pancreatic fibrosis.

In view of the fact that approximately half of our 11 cases had vomiting, noninfectious diarrhea, and moderate to marked dehydration, it is unfortunate that more thorough evaluation of body chemistry relating to adrenal function was not done. It is hoped that further reporting from other sources will reveal more information on this phase.

The presence of "inclusion bodies" within the cytomegalic cells and the apparently associated congenital anomalies have suggested a possible viral etiology, as the work initiated by Gregg leaves little doubt of the influence of certain viral diseases on the production of anomalies. Although the "inclusions" seen in cytomegaly of the adrenal gland have been likened to Cowdry Type B inclusions, we are in agreement with Dr. Henry Pinkerton (as quoted by Dr. E. L. Potter) that they probably do not represent viral inclusion bodies. It is conceivable that by physical arrangement or by artifact these formations could occur. It does not seem justified at the present time to relate cytomegaly of the adrenal gland to any known viral disease in the mother.

Cytomegalic inclusion disease of infancy (salivary gland type) may be confused with the entity under discussion because of the use of the word cytomegalic. We should like to emphasize the fact that the former is a condition of known etiology and is probably unrelated to cytomegaly of the adrenal glands. Evidence to support this is found in the dissimilar histopathology of the two. Craig and Landing were also unable to find evidence of correlation between the two conditions.

The bizarre and pleomorphic character of the cells in adrenal cytomegaly has given rise to speculation that the process might represent a neoplastic change. We have found no evidence in our own cases to lend support to this view, but Craig and Landing were impressed by the similarity between the anaplastic cells of adrenal cytomegaly and those of the masculinizing adrenal cortex carcinomas. They suggest that these cells may in some instances be precursors of the true adrenal cortex neoplasms.

Finally, since the cytomegalic changes in our knowledge have never been noted in adrenal glands removed surgically for various reasons and are seen only in the infant who comes to necropsy, the true morbidity is not known.

* Potter, E. L.: Personal communication to the authors.

SUMMARY

A review of the literature concerning the fetal adrenal cortex reveals a distinct entity, cytomegaly, of which little is known and little has been written.

We are adding 11 new cases of adrenal cytomegaly gleaned from 1243 autopsies done at the Children's Hospital, from 1942 through 1953.

Nine of the 11 cases were associated with anomalies which dated to the 5th, 6th, and 7th weeks of embryologic life.

The histology of the cytomegalic fetal adrenal cortex is described and illustrated.

Dr. H. D. Palmer gave advice and assistance and Mr. I. S. Stephens, M. T., provided the photographs.

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Aminophylline Overdosage in Children

Report of Four Cases with Toxic Symptoms

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Recent statements in the *Journal of the American Medical Association* * have raised questions concerning the occurrence of aminophylline reactions in children. Medical literature has little reference directly concerning the toxicity of aminophylline in humans and but one concerning it in children. A few cases are cited of sudden death in adults,† and Rounds [5] has published a report of six cases of severe reactions in children to the drug.

It is our purpose in this paper to report four cases in children who have had marked toxic manifestations from the use of aminophylline in the treatment of bronchial asthma and related conditions. The reported cases are of especial interest in that all were under the care of physicians and their development was observed during the course of hospitalization.

In recent years it has become common practice to employ the compounds of theophylline, usually as aminophylline U. S. P. (theophylline ethylenediamine), for their bronchodilating action in the management of certain respiratory ailments, such as bronchial asthma, asthmatic bronchitis, bronchiolitis, and obstructive tracheobronchitis. For convenience of usage, rectal administration has been more consistently utilized in the treatment of children in the form of suppositories of aminophylline alone in the vehicle base or in combinations with sedatives. In very popular current usage is a preparation which is supplied containing aminophylline, 0.5 gm., for adults, and a so-called "infant size," containing half this amount. The recommendation usually made for this product is "one at bed-time."

Theophylline, a xanthine derivative, is closely related in its pharmacologic activity to caffeine and theobromine, all three of these drugs having similar actions on the affected structures, but varying in intensity on the different structures. The chief known pharmacologic actions of the xanthine drugs are (1) stimulation of the central nervous system, (2) vasomotor and cardiovascular effects (including vasodilatation), (3) direct skeletal muscle stimulation, (4) relation of certain types of smooth muscle, such as that of the bronchial mucosa, (5) kidney action causing diuresis, and (6) gastric irritation.

Regarding the toxicity of theophylline, it may be considered with the group reactions of the xanthines. These have been experimentally demonstrated to be (1) central nervous system irritability, as shown by confusion, restlessness, excitement, and insomnia, and sensory disturbances, such as tinnitus and light flashes, the eventual result of large overdoses being convulsions followed by respiratory failure, (2) increased tension and increased reflex irritability of the peripheral musculature, (3) gastrointestinal symptoms, such as nausea, vomiting, and gastric hemorrhage, (4) marked diuresis with albuminuria leading to dehydration.

Serious or fatal reactions are probably rare in the application of aminophylline to the treatment of human disease, but it is our belief that degrees of intoxication as illustrated by the following case reports may be more common than supposed and may be overlooked or confused with the symptoms of the

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* References 1 and 2.

† References 3 and 4.

asthma or other conditions for which the drug has been given. Our cases were all under hospital observation, so it is possible to some extent to elucidate the importance of the respective roles of the reactions of the drug and the symptoms of the illness.

REPORT OF CASES

CASE 1.—J. M., a white baby boy of 15 months of age at the time of admission, on March 10, 1950, the fifth time in a series for the treatment of severe asthmatic symptoms, usually accompanied by infection varying in severity.

At the time of this admission, on March 10, 1950, the illness began acutely on the morning of entry, with sudden onset of asthmatic symptoms, fever, and nasal discharge which progressed in severity so that at the time of entry, at 9 p. m., he exhibited a dusky cyanosis and had marked respiratory difficulty.

Physical examination showed upper respiratory infection, otitis media, difficult breathing, cyanosis, and sibilant and coarse rales throughout all lung fields with almost complete suppression of breath sounds. Nutrition was good, and the child showed no signs of dehydration.

The admitting physician ordered oxygen and phenobarbital, and he gave aminophylline solution, 2 ml. (0.5 gm.) intravenously, to be followed by suppositories of 0.25 gm. every four hours.

The first aminophylline suppository was given on the following morning at 8:30 a. m., and they were thereafter given every four hours. Restlessness was noted almost immediately, and vomiting began the second day. Intake of food was poor, and fluid intake was maintained at 700 to 1000 ml. On March 13, 1950, the emesis changed in character from food and fluid to contain brownish blood admixed with mucous.

When examined at this time, the child was noted to be quite apathetic with slight muscular twitchings, but there were interspersed periods of marked restlessness. There was thought to be a moderately severe dehydration.

The administration of the aminophylline was discontinued; treatment consisted of sedation and parenteral fluids. Within three hours, the restlessness was markedly improved; the child was much more alert and became playful. The emesis ceased after the cessation of the aminophylline and the giving of fluids. The child improved continuously and was discharged on March 19, afebrile and without symptoms.

A similar reaction occurred during the next hospitalization, on April 30, 1950. On this occasion, the onset was slower, with two days of gradually increasing severity of asthmatic symptoms, a low-grade fever, and nasal discharge. The child was then admitted at 5:45 p. m. Physical findings were much the same as the previous admission except that there was no otitis present. Hydration was thought to be fair.

Treatment was begun with oxygen tent and injection of 1:1000 epinephrine chloride. The child was resting quietly, with pentobarbital (Nembutal) as a sedative, when the first aminophylline suppository was inserted, at 10:20 p. m.; this was repeated at 2 a. m. on May 1, 1950. Within a half hour, the child became quite restless and began to vomit at about 30-minute intervals. Aminophylline suppositories were continued at four-hour intervals throughout the next 24 hours. The emesis became increasingly severe and more frequent, and the patient became lethargic, almost stuporous, but slight muscular twitchings were seen.

One of us (F. M. L.) first saw the child at this time in consultation and made a presumptive diagnosis of aminophylline overdosage, based on the previous experience with this child. The aminophylline was discontinued and parenteral fluids ordered. Five hours later, the restlessness was much improved, the emesis had ceased, and the child was retaining some milk. It was thought that some dehydration was still present, and additional fluid was given intravenously. At this time the slight listlessness the child had shown improved immediately, and the infant became hungry and playful. There were no further difficulties; the patient improved continuously and was discharged as asymptomatic on May 6, 1950.

Subsequent to these two admissions, there were six additional hospitalizations for asthmatic symptoms. The admitting physician on these occasions ordered aminophylline suppositories used "if absolutely necessary" and in no case in less time than six hours. Occasionally slight restlessness occurred, but there were no further marked toxic symptoms.

CASE 2.—W. M., a white baby boy, 2 years of age, was admitted at 8 a. m., April 13, 1951, with acute bronchial asthma of several hours' duration. The child was said to have been in good health until Feb. 27, 1950, at which time he was seen by the doctor with the first of numerous episodes of rhinitis, wheezing, vomiting, and respiratory distress. Chemotherapy and "bronchodilators" were used in treatment. Hospitalizations for similar symptoms occurred on March 6, 1950, March 27, 1950, and May 12, 1950.

On the last occasion, according to the information furnished, aminophylline suppositories, 0.25 gm., were given every eight hours. There was some vomiting which responded to dietary regulation. There are no records of any urinary examinations in this series of illnesses, a point of importance to the ensuing history.

He had been seen as an office patient and treated with Syrup of Hydryllin, (diphenhydramine hydro-

chloride and aminophylline) 1 teaspoonful (4-5 ml.) four times a day. An office urinalysis done at this time showed an albuminuria of moderate grade and hyaline casts. At home the child began vomiting, and hospitalization was advised for more careful observation.

Physical examination at the time of entry revealed mild inflammation of the nose and throat membranes and typical asthmatic wheezes. Growth, development, nutrition, and hydration were not unusual. There was some distention of the abdomen and questionable edema of the legs. Blood pressure was 90/60. The white blood cell count and differential were those of infection, and albumin was again present in the urinalysis.

At the time of admission, 8 p. m., the first aminophylline suppository, 0.25 gm., was given, and in addition 0.25 ml. of 1:1000 epinephrine chloride by injection, sedation with phenobarbital, and subcutaneous fluids were ordered. A second suppository was inserted at 10:45 p. m. As the child was noted to be very restless, oxygen administration by tent was ordered. Emesis continued at frequent intervals during the night, and the child remained quite restless in spite of the oxygen and phenobarbital. As the asthmatic symptoms had abated, no further aminophylline was given on this admission, but the child continued to vomit until 8 p. m. on the night following admission. He then went on to an uneventful recovery. The urinary albumin gradually decreased and was absent on discharge, on April 11, 1951. At no time were red cells detected. Blood pressure remained normal throughout.

In the interim between this episode and the following to be described, he was again hospitalized elsewhere. At this time he was given Aminet "half strength" (aminophylline with pentobarbital) suppositories three times a day. Urinalysis at this time showed a faint trace of albumin and an occasional red cell.

The second admission to Kadlec Hospital occurred on Sept. 10, 1951, at 12:15 a. m. The physician admitting the child had seen him at home earlier on the day preceding and had ordered 0.25 gm. aminophylline suppositories every six hours; and at the time of entry he was said to have had three of these.

Physical examination on admission revealed the typical asthmatic breathing with accompanying infection. Food and fluid intake had been poor for some time prior to admission, and moderate dehydration was present.

Oxygen, phenobarbital, and aminophylline, 0.25 gm. suppositories, were ordered, and at 12:45 a. m. the first aminophylline suppository was inserted. Vomiting first occurred at 1 a. m. and continued every half hour during the night. The child had alternate periods of extreme restlessness and marked apathy. The following morning, at 11:15 a. m., 5% dextrose in saline solution was started subcutaneously. At 1 p. m., one of us (F. M. L.) was asked to see the child. By this time, he was stuporous to the point of unconsciousness except for brief periods of marked restlessness. There was deep pauseless breathing with all the accessory muscles of respiration in play. Aeration was good, and most of the wheezing was relieved. Skin turgor was poor, and the mucous membranes had a very dry appearance with normal gloss completely gone. The CO_2-combining power taken at this time was 27 vol.%.

A presumptive diagnosis of aminophylline intoxication with resulting dehydration and acidosis was made. Prompt and effective relief resulted from parenteral fluid therapy, and by 5 p. m. the child was alert, the skin warm and moist, and he was taking sips of carbonated beverages. After an uneventful recovery he was discharged with only slight residual rhinitis.

Case 3.—K. L., a 19-month-old white girl, was admitted to Kadlec Hospital at 12:10 a. m. on Dec. 5, 1951, for the fifth time, with a diagnosis of bronchial asthma, beginning 14 hours previously in this instance.

Findings on physical examination were allergic rhinitis and sibilant rales in all lung fields. The child was alert but somewhat apprehensive, and there was no evident dehydration.

An Aminet half-strength suppository had been given just prior to entry. Vomiting began at 1:15 a. m. and was repeated several times during the night. The child remained awake but was not unusually restless. The following morning the same dose was repeated, and subcutaneous fluid was administered. The child took small amounts of feeding, but vomited everything by mouth. No further aminophylline was given, and the vomiting gradually subsided. At 4 p. m. the child began to pass large semiliquid dark stools which were positive for blood. Her laboratory tests were not unusual except for a trace of albumin and 20-25 red blood cells per low-powered field in a urine taken the morning after entry. The dark stools ceased after 24 hours, and there were no further instances of emesis or intestinal bleeding.

Case 4.—H. D., a 2-year-old white boy, was admitted to Kadlec Hospital on Sept. 6, 1951, with a diagnosis of bronchial asthma, this being the fourth admission in a series for similar illness.

On the occasion of this admission, the illness began about three days before entry and became progressively worse. The child had had Syrup of Hydryllin every four hours orally, and the mother had given an injection of 1:1000 epinephrine chloride at home without response. Physical findings on admission showed typical asthmatic breathing and a mild upper respiratory infection, but the child had maintained good food and fluid intake and there was no dehydration.

The first aminophylline, as Aminet suppositories, was given at 6 p. m. At 8:10 p. m. vomiting of mucus and bile occurred. A second suppository was inserted at 11:15 p. m., following which the child became progressively more restless, and at 12:10 a. m. on Sept. 7, 1951, the character of the emesis changed to contain dark brown material which was positive for blood.

The following morning, a presumptive diagnosis of aminophylline overdosage was made by the attending physician (A. G. C.). The aminophylline was discontinued, and a subcutaneous injection of 250 ml. of lactated Ringers solution was given. Sedation was accomplished with phenobarbital. The emesis ceased during the day, and the child gradually became more comfortable. After the symptoms of intoxication subsided he made an uneventful recovery.

COMMENT

It is recognized that many of the symptoms mentioned in our cases in connection with aminophylline overdosage have been seen in connection with bronchial asthma as a disease condition. While it is not our intent to treat this latter in detail, we have briefly reviewed many of the hospital records of cases admitted with this diagnosis and find in no case any such marked and severe reactions when aminophylline was not employed in the treatment. In many instances where it had been used, occasional vomiting and moderate restlessness were noted. We think it noteworthy that in these reported cases the symptoms were uniformly related to the administration of relatively large proportionate doses of aminophylline and ceased shortly after it was discontinued.

In Case 1, dehydration was not marked, and the asthmatic condition was much relieved at the time of onset of the emesis and restlessness. In Case 2, restlessness, emesis, dehydration, and acidosis were markedly severe and constitute the most remarkable feature. The significance of the albuminuria is not clear, as it was detected before the first known administration of aminophylline. However, the blood pressure was normal at all times, and the course was not that of the usual case of nephrosis. Cases 3 and 4 are mainly illustrative of the degree of gastrointestinal irritation, which may be severe enough to result in massive bleeding.

Treatment of the condition is not difficult in the milder degrees. Cessation of the drug dosage, relief of the dehydration with fluids, and accomplishment of sedation are usually all that is necessary. We have not encountered degrees of intoxication as severe as those reported experimentally, although Rounds [5] has had instances of this degree of severity.

CONCLUSIONS

1. Aminophylline as a drug of value in the treatment of diseases which exhibit constriction of the bronchial musculature is not questioned, and it is not intended to imply that it should not be used in the treatment of bronchial asthma in children.

2. It is possible to conclude, however, that closer observation for early symptoms of toxicity should be made and that on their appearance, the aminophylline should be discontinued.

3. Dosages in children should be carefully estimated, and the "half strength" suppositories are far too strong for infants.

4. Early symptoms of toxicity which warrant cessation of the drug are unusual restlessness, recurring emesis, and any albuminuria.

5. Rectal absorption is uneven and may be delayed, and when this method is employed it calls for more careful observation.

6. Treatment of the toxicity is simple cessation of administration and appropriate relief of the symptoms.

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Progress in Pediatrics

INDIVIDUAL ANTISOCIAL BEHAVIOR

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CHILDREN from so-called good homes who recurrently steal, truant, set fires, or exhibit sexual aberrations are usually doing what their parents unconsciously wish and tell them to do.

The delinquencies under consideration are those arising in apparently "normal" families of good reputation and are not those largely determined sociologically in slums or in juvenile gangs of any economic level. This latter group often overlaps with the group I am concerned with. For years mystery enveloped the causes of such individual antisocial behavior as fire-setting, stealing, truancy, and unacceptable sexuality displayed by young delinquents or their adult counterparts, the psychopaths.

As the result of 10 years of study and concomitant treatment of the parents as well as of the child involved in the antisocial behavior, it became unmistakably evident to Szurek and me that one or occasionally both parents derive unconscious and, less frequently, conscious, vicarious gratification of of their own poorly integrated forbidden impulses in unwittingly sanctioning and fostering such behavior in the child. In every patient brought for treatment in whom simultaneous intensive study of the parents was possible, the child's defect in conscience was traceable to a like defect in the parents' own poor resolution of unconscious impulses to similar antisocial behavior. Thus, just as normal parents derive vicarious gratification from good behavior in their children, parents who, within themselves, have a poorly integrated forbidden impulse, apparently derive gratification from the bad behavior of their children. These findings led to the thesis that parents' unwitting sanction and unconscious fostering drove the child to his acts and were the specific stimuli to such antisocial behavior.

It involved long study in treatment of the parents and the child to determine precisely how the parents unwittingly communicated to the child the wish and permission to misbehave. Today it is realized that means of conveying such encouragement are innumerable. A few examples are given as follows:

1. The parents may talk about honesty but still write an illicit excuse to the school saying Johnnie was ill when this was not the case. Johnnie later uses this as blackmail to extract further concessions; this can become a vicious circle.

2. The parents may listen with an interested smile to a child's account of a misdemeanor, obviously enjoying it. No spanking at the end will undo the pleasure the child sensed he gave the parents in the narration, and he will repeat the misdemeanor.

3. One cannot teach a child about honesty with money and condone his getting into the movie for half price when he is over-age, nor will he listen to any precepts about financial honesty when he hears one parent gloat over shortchanging the grocer.

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Work represented in this paper was carried out by Dr. Johnson and Dr. S. A. Szurek at the Chicago Institute for Juvenile Research, University of Illinois, the Chicago Institute for Psychoanalysis, the Mayo Clinic, and the Langley Porter Clinic.

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4. One cannot create rigid guilt in a child about fires if the parent tells the child to stop playing with fires but adds, "If you must get it out of your system then set some fires in the kitchen sink." Fires are taboo every place except in stoves and fireplaces or for a cigarette or candles.

5. One cannot teach guilt about sexual misbehavior in adolescents by suggesting alternative antisocial modes of behavior in terms of dire warnings, suspicious questions, or listening with avid interest to indiscretions. No punishment after such obvious interest will do any good. In truth, as time goes on, the child senses that the parent shows gratifying interest in misbehavior and indifference to much of the good behavior. The child then complies with the parent's deep interest in misbehaving.

6. Jimmie, who is learning at 5 years of age that nobody can take another's money, cannot be expected to acquire a good conscience when he is told, "If you keep this up, you will end in jail." He then senses that this prognostication is the alternative and possible view of him.

7. Playing with or going into anyone's pocketbook, including that of the parents, must be tabooed early, but this admonition is weakened when the young child is asked to get money from the parent's purse instead of bringing the pocketbook to the owner.

8. Children cannot be taught integrity and the virtue of truth if promises are broken without a sincere apology and the unexpected turn of reality explained to the child.

These few illustrations depict a technique of vacillating prohibition and permission that never can constitute a rigid setting of limits.

ENLISTMENT OF A SCAPEGOAT

One child is selected unconsciously as the scapegoat to live out the loophole in the parents' own conscience and their unconscious drive toward antisocial behavior. This child may be the only one selected to be the scapegoat in a family of several children, the others being exempted and consequently well behaved. An adopted child may be particularly suitable for such a role, since the encouraged misbehavior may be attributed to heredity rather than to parental encouragement. The young boy who was born when a girl was badly wanted, or the younger of two sons who superficially resembles the younger of two uncles who was "spoiled and no good from the start," is a likely candidate. Formulas for the unconscious selection of the unfortunate scapegoat are as multiple as are the devious patterns for impressing him into his tragic role.

EMERGENCE OF CONSCIENCE

A child's conscience is made, not born. A child attains this through identification with and mimicry of the parents, especially in the first six or seven years of life. This identification or mimicry embraces both conscious and unconscious operations of the parents. Normal parents never even doubt that their children will become honest and learn the right of private property. They have no fears of their children later stealing, setting fires and engaging in vandalism or any highly destructive behavior toward life and property because the taboos and guilt in themselves about these matters are as rigid as granite and correctly so. This was true of their great-grandfathers, and it is true today. Such normal parents are neither checking detectives, putting ideas into a child's head, nor lax condoners. Just as children are not permitted the experience of dashing in front of cars or testing out poisons, they are rigidly denied the indulgence of fire-setting, vandalism, or stealing. There can be no cutting corners and no hedging on such issues. This is the core of conscience.

Paralyzed consternation may overtake a parent whose 7-year-old has just taken a dollar from the dresser or displayed a trinket pilfered from the dime store. Why this anxiety, confusion, or even undue hostility? Why not manage the matter firmly and directly? There is a reason. An impulse in the parent, alternative to complete honesty, compels vacillation and hedging rather than the establishment of a clear limit. That im-

pulse may explode into a rage, with threats of the reformatory. Such a parental reaction suggests to the child that his impulses to steal really may get out of hand.

The mature normal parent neither anticipates impending disaster nor dismisses monetary transgressions as trivial. Instead, the problem is resolved promptly without anxiety or guilt. Of the dime-store trinket the mother tells Johnnie firmly and without anxiety that it is wrong to take things without paying for them. She accompanies Johnnie to the store to return or pay for the article. Storekeepers are accustomed to parents coming on such errands and usually accept the proper restitution. The parent does not dismiss recurrent minor thefts with the rationalization "Oh, he will outgrow it," only to bring the child for treatment when the school complains of thefts at a later age. There are many variations on the main theme that deception encourages deception, such as the admonition of the mother who says to the child, "Here is a dollar, but don't tell your father."

The psychopathic personality or "psychopath" of later years is the grown-up delinquent child with defects in conscience, who is in court for theft, burglary, forgery, or worse. In every such instance providing opportunity for careful study, a long history is revealed of parental sanction of antisocial offenses and intervention through "bailing out" and "fixing."

A rigid conscience about antisocial behavior is the greatest heritage parents can give a child. A shambles of a conscience in the end destroys the child and concomitantly the parent who had unwittingly fostered the defect in the unconsciously disliked child.

TRUANCY AND DESTRUCTIVE BEHAVIOR

Parental coldness and rejection are insufficient causes of truancy from home. These attitudes are nonspecific stimuli to which many children who do not run away are also exposed. Truancy usually results from suggestion at home, sometimes relatively overt, sometimes disguised and difficult to detect.

All persons have detected certain amusing aspects in a child's unwise adventure as he relates it. Conscious of the dangers inherent in such an adventure, the wise adult easily controls any sign of amusement and concentrates on the gravity of such behavior. Some adults, however, are so intrigued by a child's doing certain dangerous or antisocial things that the most intense interest and gratification are communicated to the child during the narration. A parent, describing his child's vandalism, may reveal by the amused excited expression on his own face and by his histrionic pantomiming that he is achieving intense gratification from this daring misbehavior. Children are masters at sensing parental interest or gratification, however subtle, at a tale of naughtiness. Even if punishment comes after the interest-arousing narrative, the damage has been done, for the child wishes to comply with that aspect of the parent which revealed deep gratification.

SEXUAL MISBEHAVIOR

The same pattern of selection of a scapegoat, choice of misbehavior to be suggested, and subtle guidance of the child into antisocial activity is seen in sexual misbehavior. Again, the variants of the theme are multiple. Parental suspiciousness or acute anxiety coupled with an expression of eagerness suggests to the child that alternate forms of behavior may well occur on adolescent dates and might even be accepted; inordinate maternal curiosity and interest regarding the daughter's experiences with boys carries not only implied sanction but a maternal need for gratification through the daughter. Knowledge of parents' extramarital affairs pushes the adolescent child into sexual acting out. Misguided and inordinately exciting discussions with parents about sex constitute unwitting approval; encouragement or display of undue degrees of nudity at home provides excessive permission. Illustrations are endless.

It is amazing to discover the extent to which intelligent families of respectable status accept and even encourage varying degrees

of nudity, including the complete variety, with conversion of the bathroom and its gamut of functions into a traffic resembling a public thoroughfare. This attitude is accompanied by a "frankness" regarding procreation and its antecedent ramifications carried far beyond the needs of the curious child.

MALIGNANT SEQUELAE OF EXTREME FREEDOM AND FRUSTRATIONS

The degree to which "freedom" is practiced in the best of families is remarkable. Mothers who, under the guise of motherliness, take to bed with them male children who are well beyond infancy and even into adolescence, or fathers whose caresses of adolescent daughters slightly exceed paternal affection only store up unconscious rage in the child because he is unconsciously stimulated.

The emotional sequelae flowing from such combined permission and frustration are as predictable as those from the administration of thyroid hormone to a normal person. Too often the situation leads to a psychiatrist's office, a state hospital, or a newspaper headline. Nothing is mysterious about the cause of individual hostile sexual crimes when psychiatrists have a chance to study the parents as well as the offender.

MANAGEMENT OF INDIVIDUAL DELINQUENCY

The evidence for the propositions expounded here, or, more properly, illustration of the facts recounted, lies at hand in every case of individual antisocial behavior in the nonsociologic group of delinquencies. The persons under consideration are psychiatric problems. The evidence for the difficulties in these persons must be sought with diligence, gentle persistence, and skill, usually by two therapists collaborating closely. Only the experienced observer will detect the clues and pursue them with such oblique and subtle questioning as will yield the truth. Direct questioning is usually fruitless. Unearthing of parental sanction of antisocial behavior in children is one of the most formidable challenges that confront psychiatrists. Unless the child can be separated from the parents for a long period during psychiatric treatment, only collaborative treatment of the significantly permissive parent or parents and the child will ameliorate the situation.

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MOST IMPORTANT SKIN DISEASES OF CHILDREN

Their Diagnosis and Treatment

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SKIN DISEASES in children often differ sufficiently from those seen in adults to warrant special consideration. We consider the following the commonest skin diseases in infants and children *:

Alopecia areata	Molluscum contagiosum
Birthmarks (hemangioma)	Pediculosis
Contact dermatitis	Pityriasis rosea
Diaper rash	Pyodermas
Herpes simplex	Ringworm (tinea)
Impetigo contagiosa	Scabies
Infantile eczema	Seborrheic dermatitis
Insect bites	Urticaria
Keloid	Warts
Moles (pigmented nevi)	

ALOPECIA AREATA

Diagnosis.—Alopecia areata consists of round hairless patches; the involved skin is normal in appearance or slightly scaly. The patches may be single or multiple. The alopecia may extend all over the scalp to produce what is called alopecia totalis. The condition may also affect eyebrows and axillary and pubic hair. It is important to rule out superficial ringworm of the scalp; a check of the scalp with Wood's light usually makes the differentiation easy.

Treatment.—A stimulating ointment containing 3% betanaphthol, 3% salicylic acid, and 6% sulfur in a washable cream may be applied twice a day. Ultraviolet treatment seems helpful in more resistant cases. Patients with total alopecia should be checked for foci of infection. Thyroid has been successful in some cases of total alopecia. Cortisone produces only temporary regrowth; the hair falls out again when the drug is withdrawn.

Prognosis.—The localized forms usually recover spontaneously, but recurrences occur. In total alopecia the prognosis is usually poor, although some children regain all of their hair.

BIRTHMARKS (HEMANGIOMAS)

Diagnosis.—The two commonest forms of birthmarks in children are the elevated tumor-like hemagiomas called "strawberry mark" and the flat so-called "port-wine mark," or nevus flammeus. They may be present at birth or show up during the first two weeks of life. When hemangiomas occur in premature children, ophthalmoscopic examinations are indicated because of the possible association with retrolental fibroplasia.

Treatment.—Many but not all strawberry marks disappear completely by the time the child reaches the age of 6 years. In the case of slow-growing hemangiomas, especially when located on cosmetically unimportant sites, one may adopt a "wait and see" attitude, providing the parents are willing to take the chance. However, it is advisable to treat every hemangioma which is located around the mouth, vulva, or rectum and those hemangiomas which grow rapidly, because they have a greater tendency to ulcerate; in some instances this may lead to severe tissue defects.

Treatment of elevated hemangiomas is harmless and usually very successful if handled by an expert. It should be started before the child is six months old. The method of choice is radium, but only gamma

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* Acne vulgaris is not discussed because it is a disease of adolescents and younger adults.

rays should be used. For larger hemangiomas, roentgen irradiation is a simpler procedure. Surgery is rarely indicated. Carbon dioxide snow, in the hand of the experienced operator, can do a very satisfactory job for the smaller, more superficial hemangiomas.

Mild forms of "port-wine" marks need no treatment when hidden; the more or less V-shaped marks in the center of the forehead often fade out spontaneously. Treatment of the severe dark bluish-red port-wine stains is not too satisfactory. Radium and conventional x-rays should never be used. Abrasion by sandpaper has been recommended by some; grenz rays (Bucky rays), by others. Our method consists of the application of thorium X in a lacquer base. Complete disappearance of a nevus flammeus is exceptional, but most cases improve to such a degree that patients and parents are satisfied. Where no treatment is used, or where treatment has failed, the nevus can be covered by a special cream called Covermark.

CONTACT DERMATITIS

Diagnosis.—Contact dermatitis should be suspected in every instance of an acute dermatitis, especially when it occurs on the exposed parts or when a dermatitis appears during the treatment of another dermatosis. It is found less frequently in children than in adults. The main causes of contact dermatitis in children are probably medication and poison ivy. The latter often produces a bullous eruption.

Treatment.—Contact with the causative agent must be avoided. The treatment is usually the same as that outlined under the heading "Infantile Eczema." Antihistamines given internally often relieve the pruritus. In the hyperacute and generalized contact dermatitis, one may try cortisone for a few days if the conventional treatment fails. Poison ivy dermatitis should not be treated with injections of poison ivy extract while the eruption is present. These injections often severely aggravate the condition. However, prophylactic treatment, either orally or by injection, often helps; it should be started early in the year.

DIAPER RASH

Diagnosis.—"Diaper rash" is a term applied to an eruption of the diaper region, which may range from a simple irritation to a persistent secondarily infected dermatitis. This condition is thought to be due to the ammonia released from the urine by bacterial action.

Treatment.—In mild cases it suffices to change the diapers frequently, boil them, and rinse them in an antiseptic, such as methylbenzethonium (Diaparene), which does not contain boric acid.† In severer cases, the treatment for infectious infantile eczema usually helps. The new protective silicone preparations (Pro-Derna, Silicote) are helpful in resistant cases; they are applied twice or three times a day and may also be used in milder cases.

HERPES SIMPLEX

Diagnosis.—Herpes simplex is a virus infection which usually appears as grouped vesicles of the face, especially around the mouth. In children, herpes simplex often appears first as a severe stomatitis accompanied by regional lymphadenopathy and fever; scattered vesicles may also occur on the skin. A severer form of herpetic infection of children, especially infants, often fatal, is so-called Kaposi's varicelliform eruption; this is usually superimposed on infantile eczema. The face and other parts of the body are covered by vaccinia-like lesions.

Treatment.—Localized herpes simplex is best treated with some antibiotic ointment of a type which is not given systemically; this will prevent secondary infection. If there are frequent recurrences, smallpox vaccinations are often effective; at least they may prolong the interval between recurrences. We repeat the vaccination four to six times at two-week intervals. The severer forms of herpes simplex, especially Kaposi's varicelliform eruption, should be treated systemically with sulfonamides or antibiotics to

† The use of boric acid in infants is frowned upon by many pediatricians because of its potential toxicity. We do not use it for babies and infants.

keep down the secondary infection; local application of 1% aqueous methylrosaniline chloride (gentian violet) is helpful in these cases.

IMPETIGO CONTAGIOSA

Diagnosis.—Impetigo contagiosa is a pyogenic infection which frequently affects children, predominantly on the face. There are different forms of impetigo contagiosa:

1. Streptococcic impetigo is characterized by heavy yellowish, sometimes bloody, crusts. It is contagious, although less so than the staphylococcic form. Not infrequently, the crusted impetigo is found secondary to other conditions, such as a cold sore, eczema, or scabies.

Ecthyma is but a deeper form of the streptococcic impetigo, which penetrates and destroys tissue beyond the epithelium. It consists of crusted, more or less superficial ulcerations of the lower legs. For this reason, ecthyma is usually followed by scars, while simple impetigo is not.

2. Staphylococcic impetigo is characterized by flat brownish crusts and flat blisters, which sometimes resemble ringworm. This impetigo is very contagious.

Bullous impetigo is also caused by the Staphylococcus, but it is especially found in newborn babies and infants. It is often called pemphigus of the newborn.

Treatment.—The modern antibiotics have simplified the treatment of the various forms of impetigo. Most cases respond to the local application of neomycin ointment. In severer cases, oral or parenteral antibiotics should be used.

In bullous impetigo of the newborn, ointments are usually contraindicated because they aid in the maceration of the skin. The blisters are opened and 3% to 5% silver nitrate or 1% aqueous methylrosaniline chloride is gently applied; this is followed by a mild antiseptic powder such as the following:

	gm.
Dermatol (bismuth subgallate)	1.5
Zinc oxide powder	3.0
Talc, q. s. ad	30.0

S: Apply 3 times a day.

Do not bathe or oil the baby. Wherever the infection is serious, internal antibiotics should be given and the babies hospitalized. The urine should be checked in all cases of impetigo, since occasionally nephritis occurs.

INFANTILE ECZEMA

The term "infantile eczema" includes atopic dermatitis (the so-called allergic eczema), seborrheic dermatitis, contact dermatitis, and infectious eczemas; combinations of these forms of eczema occur.

The distinction between the various forms of eczema is not always easy. However, most eczemas that begin before the age of 6 months, that lead to scratching, and that are persistent belong to the atopic eczema.

Infantile Atopic Eczema.—Diagnosis: In infants, a weeping eczema of both cheeks with thickening of the skin is characteristic; often the antecubital and popliteal spaces and the wrists are involved; in severer cases the eczema may cover most, or all, of the skin. In eczema the skin is the shock organ of various insults—allergic, infectious, nervous, and emotional. Allergic factors—foods as well as environmental allergens—have to be considered. The most important food allergens in our experience are wheat, potatoes, and milk; cattle, house dust, and feathers are the most important environmental allergens. Skin tests are often helpful, in regard to both food and environmental allergens. We perform scratch tests nearly exclusively; only when they are negative do we do a few intradermal tests.

Treatment: Unless we suspect milk allergy, the diet consists of milk (evaporated), oatmeal, rice, carrots, and pears. New foods are added at three- to four-day intervals. Synthetic vitamins are given, and vitamin B is added in large amounts, such as White's Multibeta, 15 to 25 drops three times a day. The child is placed in an environment as dust-free as possible.

Local treatment must be applied according to the stage. In the acute phase mild treatment, such as wet compresses with aluminum acetate, soda, or matricaria (chamomile) are recommended. In cases of second-

ary infection, we use potassium permanganate, 1 : 9000. We alternate these compresses with the application of a mild oily lotion of the following composition ‡:

Ichthammol (Ichthyol, Schering Corporation) .....2.4 gm.
Zinc oxide.....48.0 gm.
Corn oil (Mazola), q. s. ad.....120.0 cc.

When the eczema improves, coal tar is the drug of choice; 3% coal tar in zinc oxide ointment is applied with a bandage, or a tar lotion without a bandage. We routinely incorporate an antiseptic such as 1% hexachlorophene or 1% Rivanol (2-ethoxy-6, 9-diamino-acridine lactate), or we use one part of neomycin ointment to two parts of the tar ointment. It is advisable to use the tar first on a small area only to make sure it is well tolerated. In less severe cases an ointment of 3% ammoniated mercury in zinc oxide is often helpful, or a mixture of Myciguent ointment (an emulsion-type ointment containing neomycin sulfate) and chlorcyclizine (Perazil) cream.

Local application of hydrocortisone ointments is helpful in chronic cases; this medication, apparently harmless, is clean but expensive. In very severe cases, oral cortisone is of help. As we do not know enough about the potential risk of this treatment, we use cortisone or corticotropin (ACTH) in emergencies only. We have rarely needed cortisone in the management of infantile eczema.

Soaps and baby oils are often well tolerated. When these are irritating, however, modern sulfonated oils or other soap substitutes are tried.

For restlessness, 1/8 to 1/4 grain (8 to 15 mg.) phenobarbital t. i. d., or as needed, is given.

Antihistamines have been disappointing.

‡ In case of secondary infection we add 2% hexachlorophene (G-11), as an antiseptic, to the lotion. The formula then is as follows:

10% hexachlorophene in corn oil.....24.0 cc.
(Ar-Ex Cosmetics, Chicago)
Ichthammol (Schering Corporation)....2.4 gm.
Zinc Oxide.....48.0 gm.
Corn oil (Mazola), q. s. ad.....120.0 cc.

Severe cases should be hospitalized. In the presence of a more outspoken secondary infection, systemic antibiotics should be given. Psychologic factors should not be overlooked. Often the behavior of the child or the mother gives a clue in this direction.

Infantile Seborrheic Dermatitis.—Diagnosis: In its pure form it appears as "cradle cap," or roundish patches on cheeks or trunk. But in most instances it is combined with atopic eczema.

Treatment: Not infrequently some underlying systemic condition, such as malnutrition or secondary anemia, is present and must be treated. We favor large amounts of vitamin B complex. Locally 2% or 3% ammoniated mercury in zinc oxide ointment is often all that is needed. In more stubborn cases, one may use a tar ointment, as described above, or 5% sulfur in zinc oxide (Lassar's) paste.

Infantile Contact Dermatitis.—Diagnosis: When the eczema originates in parts other than the face, contact dermatitis should be suspected. Underwear, plastic diapers, medications, soaps, baby oils, and other sources of contact should be investigated and the offending contact avoided.

Treatment: Mild local treatment usually suffices when the causative factor has been eliminated.

Infectious Infantile Eczema.—Diagnosis: This form is usually encountered as intertrigo, a weeping acutely irritated dermatitis of the folds of the neck, axillae, groins, and antecubital and popliteal areas; mostly it is sharply outlined. It is caused by bacteria or fungi.

Treatment: The treatment of the acute phase is the same as in other eczemas. In resistant cases, 1% aqueous methylrosaniline chloride is a very helpful, though messy, remedy. After the acute stage subsides, we use 2% iodochlorhydroxyquin (Vioform) incorporated in petrolatum or in zinc oxide paste.

Eczema in the older children presents similar problems. In the atopic form, skin tests, as well as allergic factors, become less

significant as the child grows older. Local and also psychologic treatment becomes more important.

INSECT BITES

Diagnosis.—Insect bites usually occur on exposed areas of the skin. Often, however, especially in smaller children, the symptoms are atypical and may produce large wheals, even blisters. Another atypical form is that of those papular lesions called lichen urticatus. This eruption in many instances apparently is an allergic reaction to insect bites.

Treatment.—The pruritus can be relieved by the internal use of antihistamines, as well as by the local application of antihistaminic and anesthetic ointments. Most of them are sensitizers and must be used with caution. Chlorcyclizine cream and dimethisoquin (Quotane) lotion probably have the least sensitizing effect of any of these preparations. In cases of secondary infection, bacitracin or neomycin should be applied. For prevention, 6-12 (2-ethyl-1,3-hexanediol) is a very effective repellent for mosquitos, but it should not be used close to the eyes. Where the bites are due to home-born insects, careful spraying of the home with dichlorodiphenyltrichloroethane (D. D. T.) should be done.

KELOID

Diagnosis.—Keloids are essentially hypertrophic scars, though at times no preceding trauma seems apparent. They occur frequently after burns. Small keloids usually do not produce any symtoms, but at times they do itch. Large keloids, especially following burns, frequently cause contractures and inhibit motion.

Treatment. — Minor keloids — especially following surgery—may regress spontaneously. If treatment is required, either for cosmetic reasons or because of impaired motion, the gamma rays of radium or x-rays are the methods of choice. This treatment has to be carried out by a qualified dermatologist or roentgenologist.

If the radiotherapy does not relieve the contracture, plastic surgery is indicated. It is advisable to wait several years, because frequently surgery then can be performed without much danger of additional keloids.

MOLES (PIGMENTED NEVI)

Diagnosis.—Most moles occur as small, more or less pigmented lesions, either flat or raised. The overwhelming majority of these moles are harmless and do not require any treatment.

Treatment.—There are two indications for treatment—moles which grow rapidly or show change in color or texture should be completely excised and microscopically examined. The other indication is for cosmetic reasons. Where excision would leave too much of a scar and when one is sure of the benign nature of the nevus, destruction with the electric needle or removal of the protruding portion by scissors, followed by electrodesiccation, is the treatment of choice.

Larger pigmented moles, which at times cover a great part of the body, constitute serious cosmetic problems. Plastic surgery has most to offer. X-ray and radium should never be used in any type of pigmented nevi, because these moles are radioresistent.

MOLLUSCUM CONTAGIOSUM

Diagnosis.—Molluscum contagiosum is a virus disease manifested by blister-like lesions usually 1 to 5 mm. in diameter. They have a doughnut shape, with a waxy whitish edge and a darker-colored center. The commonest sites are the face and arms.

Treatment.—Where only a few lesions are present, incision with a fine knife and expression of the contents, followed by application of iodine tincture, is sufficient. In extensive cases chlortetracycline (Aureomycin), given internally, may be tried.

PEDICULOSIS

Diagnosis.—Three different varieties of lice are responsible for pediculosis of the head, of the body, and of the public area, respectively. In children, we practically deal only with pediculosis of the scalp. The symptoms may be only pruritus, or there may also be an eczema of the nape of the neck. Demonstration of the louse or the nits is diagnostic.

Treatment.—Gamma benzene hexachloride (Kwell or Gamiso ointment) and dichlorodiphenyltrichloroethane are very effective. If they fail, Cuprex (a proprietary copper preparation) may be used. In persistent cases, one should look for sources of reinfection.

PITYRIASIS ROSEA

Diagnosis.—Pityriasis rosea usually begins with a primary patch, the so-called "herald spot," an oval scaling erythematous lesion of a pinkish-yellowish color, which may reach a few centimeters in diameter. Within a week or two this is usually followed by similar, but smaller, patches on the trunk and limbs. The face is usually spared; involvment of the scalp is rare.

Treatment.—The disease is self-limited and usually runs its course in about two months or less. No specific therapy is known; often none is needed. Locally a mild antipruritic cream or lotion is helpful. Antihistamines are helpful when the pruritus is severe. Ultraviolet irradiation in erythema-producing doses may be used in resistant cases.

PYODERMAS

Diagnosis.—Furuncles, or "boils," are the commonest pyodermas in childhood. They are infections of the hair follicles or sweat glands due to Staphylococcus aureus. Most often they occur in children who are below par.

Treatment.—An attack of furunculosis will yield easily to antibiotics, parenterally or orally. The individual furuncle should be drained by a small incision and covered with a mild antiseptic ointment (ammoniated mercury, neomycin) to prevent spreading of infection. Recurrent furunculosis often yields to treatment with a staphylococcic vaccine.

RINGWORM (TINEA)

Tinea Capitis (Ringworm of the Scalp).—There are two main varieties: (1) the superficial form and (2) the deep fungus infection of the scalp, called kerion of Celsus.

Superficial Form: Diagnosis. The superficial, usually noninflammatory, type consists of round spots of broken-off hairs with gray scales. This type occurs as an epidemic among children, is highly contagious, and is very resistant to treatment. The causative fungus most frequently is Microsporum audouini. As the infected hairs fluoresce greenly under the Wood light, the diagnosis is easy even in early cases. There are, however, other fungi causing superficial tinea capitis which do not produce fluorescence. Microscopic and cultural examination therefore is necessary.

Treatment. If not treated, this form of tinea may persist for many years but frequently clears up during puberty. For generalized or resistant cases, the most effective treatment consists of x-ray epilation § combined with proper local treatment. Yet many cases can be cured without x-ray therapy, although it usually takes much longer. Many "fungicidal" ointments have been recommended. Among the newer ointments, Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) and zinchlorundesal (Salundek) seem useful, but none is ideal. It is important to prevent spreading of the infection.

Kerion of Celsus: Diagnosis. There are granulomatous lesions of various sizes which protrude 1 to 2 cm. beyond the surface of the skin and become secondarily infected and painful. It is an alarming sight for the parents. The condition clears up after many weeks or months, even without treatment. The most commmon causative fungus, particularly in rural areas, is Trichophyton gypseum, contracted from animals.

Treatment. The more acutely inflamed the condition is, the milder the treatment has to be. Wet compresses and applications of a mild antiseptic ointment are recommended. The secondary infection can be relieved by the internal use of antibiotics or sulfonamides. When the acute phase is subsiding, x-ray therapy often is helpful in speeding up recovery and apparently also has a beneficial effect on the resulting scar. The parents

§ X-ray epilation should be carried out only by a dermatologist or roentgenologist who is familiar with the special technique.

should be reassured that the condition almost always turns out well; however, in many instances the hair will not grow back at the site of the ringworm.

Tinea Corporis (Ringworm of the Body).—Diagnosis: Ringworm of the body usually consists of inflammatory plaques which have a tendency to progress in the periphery and to heal in the center.

Treatment: We use 2% iodochlorhydroxyquin in equal parts of alcohol and ether, alone or followed by either 3% iodochlorhydroxyquin or 3% salicylic acid and 6% sulfur, or zincundecate (Desenex) or Asterol ointment.

Dermatophytosis of Feet and Hands ("Athlete's Foot").—Diagnosis: This condition originates most frequently between the toes or on the sole of one foot and may vary from scaling and slight maceration between the toes to an acute vesicular dermatitis of the feet, with or without generalized eruption usually called a dermatophytid. The latter may be accompanied by general malaise and fever and present a picture which at times is mistaken for scarlet fever. However, not all cases of eruptions of the feet are fungus infections; one must also consider contact dermatitis from shoes or socks or poison ivy dermatitis.

Treatment: The treatment is the same as for an infected acute dermatitis, described previously. In the acute eruptions wet compresses of Domeboro (aluminum acetate preparation) tablets or powder are used. Later, a mild ointment, such as zincundecate, Timofax (an undecylenate preparation), or 2% iodochlorhydroxyquin petroleum may be used at night and a powder such as Quinsana during the day.

SCABIES

Diagnosis.—Scabies is caused by a mite, Sarcoptes scabiei. Pruritus, especially at night, is the most important symptom; excoriations and crusts and secondary infection are commonly found. Often, more than one member of a family is afflicted. The diagnostic lesion is the burrow, which is found most frequently between the fingers. Usually the clinical picture is sufficient. However, pinworm infestation may produce similar eruptions, although usually more pronounced on the buttocks and legs. The microscopic demonstration of the mite, or its eggs, clinches the diagnosis. Other members of the family should be examined for scabies.

Treatment.—Scabies in children is usually more resistant than in adults. Gamma benzene hexachloride (commercially available as Kwell and Gamiso) is the ideal treatment. These ointments are clean and nonirritating, combat secondary infection, and can be used even in the presence of a dermatitis. It is advisable to prescribe a second course of therapy after two weeks.

SEBORRHEIC DERMATITIS

Diagnosis.—In the older child— in contrast to infants ‖—seborrheic dermatitis presents the same picture as in adults: dry or oily scaliness of the scalp, at times with an erythematous border, especially at the hairline. On the body, the yellowish roundish or polycyclic patches, especially over the sternum and between the shoulder blades, are typical. Often the skin behind the ears and the ear canals are involved. These areas often become secondarily infected.

Treatment.—Mild cases respond to 3% ammoniated mercury in zinc oxide ointment applied to the body and in a washable cream for the scalp. A 2% salicyclic acid-3% colloidal sulfur cream in a washable base often is helpful in either location. Vitamin B in large amounts and also iron are helpful in many cases.

The scaly seborrhea of the scalp, commonly called dandruff, responds very well to selenium (Selsum) sulfide; however, as selenium sulfide is very toxic, the material must be kept out of reach of children.

URTICARIA

Diagnosis.—Urticaria in children is usually less difficult a problem than in adults. The clinical picture is the same; in most instances we have only hives, but angioneurotic edema may accompany severer cases.

‖ See section on infantile eczema.

(1) Allergic Urticaria: Frequently there is a history of a previous, often milder, attack. These cases of acute urticaria are usually due to foods or drugs. A careful history is most important. Often it is not possible to find the responsible food at the time of the first attack, but by alerting the mother to the possible causes and by keeping track of the child's diet, the parents themselves may find the cause. Among the drugs that cause hives in childhood, cough drops rank first in our experience.

(2) Infectious Urticaria: This is a more chronic form. The attacks are daily, or nearly so, but there is no rhyme or reason. Some days are much better; then there is a severe new eruption. Often the onset of this form of urticaria can be traced to an infection, usually of the upper respiratory tract.

Treatment.—In allergic urticaria, avoidance of the allergen is important. The antihistamines will relieve most cases of acute urticaria. Local treatment often is not needed. Plain calamine lotion with 10% Calmitol (camphorated chloral, hyoscyamine oleate, and menthol) may be helpful. Sedation for the child and the mother seems necessary at times. In infectious urticaria, treatment of the underlying infection with antibiotics or sulfonamides is usually successful.

WARTS

Warts occur in children in three forms: juvenile warts (verruca plana), common warts (verruca vulgaris), and plantar warts.

Juvenile Warts (Verruca Plana).—Diagnosis: These warts usually consist of numerous very flat more or less polygonal lesions of a reddish-yellow color. Commonest sites are the face, hands, and lower arms. The diagnosis of this type of wart is difficult at times because of secondary inflammation.

Treatment: The method of choice for treatment of juvenile warts is psychotherapy¶; in our experience this method is almost always successful in juvenile warts. It is unfortunate to see children and young adults whose verrucae planae have been treated with the cautery or strong chemicals and who are left for life with unsightly scars which could have been avoided.

Common Warts (Verruca Vulgaris).—Diagnosis: This is the "warty" type so often seen on the hands of children, although it may occur any other place.

Treatment: Psychotherapy is less effective than in juvenile warts. Where the scar does not matter, curettage and superficial electrodesiccation is the fastest treatment. When they are located at the dorsum of the hands, especially around the nails, we prefer the repeated application of a 40% salicyclic acid tape for four days, either alone or followed by an application of a 40% formaldehyde ointment in Aquaphor (proprietary skin-detergent ointment containing hydroxyl animal fats). This treatment takes time, but can be carried out by the mother at home.

Plantar Warts.—Diagnosis: Plantar warts are often mistaken for calluses or corns. With a magnifying glass one is often able to see the characteristic brownish dark "spots" of the plantar wart. Warts are usually more tender and inflammed.

Treatment: X-ray treatment in the hand of the expert is often helpful. The treatment with formaldehyde, or salicyclic acid tape and formaldehyde ointment as described above, although taking longer, is often preferred by the patients. Curettage and electrodesiccation carried out by someone experienced in this treatment is an excellent method.#

REFERENCE

1. Verruca Plantaris in Current Therapy 1951: Latest Approved Methods of Treatment for the Practicing Physician, edited by H. F. Conn and others, Philadelphia, W. B. Saunders Company, 1951.

¶ Reference 1, p. 491.

Reference 1, p. 492.

Case Reports

GANGRENE OF THE GALL BLADDER DUE TO TORSION IN A NINE-YEAR-OLD CHILD

JOHN H. BOGLE, M.D., Loup City, Nebr.

GANGRENE of the gall bladder due to torsion is a fairly rare condition, the reported cases occurring mostly in adults and elderly persons.[1] Rawson [2] has recently reviewed the literature of the subject as applied to children and reports the case of a 12-year-old boy who survived operation. At that time this was the youngest case in the world literature described in the English language. The following case, of a 9-year-old boy who was successfully operated upon, is deemed of sufficient interest to report.

REPORT OF CASE

E. Y., a 9-year-old boy, was first seen at the Loup City Clinic on June 17, 1954. At that time he was complaining of moderately severe pain in the right upper quadrant of the abdomen. This had begun five hours previously, and vomiting had occurred several times.

The parents of the child stated that for about two years he had complained of recurrent attacks of abdominal pain, which were relieved by lying down.

Upon examination the patient was seen to be a wiry active boy 9 years of age. The abdomen was not distended. There was moderate tenderness present in the right upper abdominal quadrant, without spasm or rebound pain. His temperature was 98.0 F. The tongue was moist, and the pulse was not rapid.

No definite diagnosis was made at this time, and the findings were not considered to be sufficient to warrant admission to the hospital. The parents were advised to bring the child back the next day if the symptoms continued or became worse.

He was brought back two days later, on June 19. The parents stated that the pain had been intermittent during this interval, and that at times he had seemed well. However, recurrence of pain and vomiting had taken place, and the abdomen had become quite tender in the past few hours.

Examination at this time revealed a moderately ill boy. The face was flushed and the tongue somewhat dry. The pulse was rapid and the temperature 99.8 F. The abdomen was slightly distended. Marked tenderness, spasm, and rebound pain were present in the right upper quadrant. No mass could be felt. The white blood cell count was 18,250, with 74% polymorphonuclears, and the urinalysis was normal. A diagnosis of acute appendicitis in a high-lying appendix was made, and the patient was admitted to the Sacred Heart Hospital for operation.

The operation was performed under general anesthesia. The abdomen was entered through a right upper quadrant transverse incision. The gall bladder was found to be lying free, without adhesions. It was totally black in color and was attached only by the cystic duct and a short mesentery 2 cm. long on the cystic duct. The usual attachment of the gall bladder by peritoneum to the liver was absent, so that the organ could easily twist on its small pedicle. In exploring the region, when the hand was first inserted into the abdomen, the torsion was relieved, and it untwisted as the gall bladder was lifted up.

The cystic duct and the cystic artery were dissected out and separately ligated and cut. The short mesentery on the cystic duct was then cut, and the gall bladder was removed. The field was dry, and there was no fossa to suture. Appendicectomy was performed. A Penrose drain was inserted into Morison's pouch and the wound closed in layers.

The postoperative course was quite smooth. He was discharged on the ninth day with the wound well healed. Since then the patient has been seen several times, and he is entirely well.

Pathology Report (John R. Schenken, M.D., Omaha, Nebr.).—The gall bladder is intact and measures $6 \times 3 \times 2$ cm. Upon being opened, it is found that its lumen is completely devoid of bile and calculi. The mucosa appears replaced by friable, greenish-brown material, and the adjacent wall, measuring up to 0.5 cm. in thickness, has a firm, moist, purplish-gray appearance throughout.

Microscopic examination of sections of the gall bladder reveal the wall and mucosa to be infarcted and diffusely hemorrhagic. There is also associated chronic and acute inflammatory cell infiltration. Diagnosis: Infarction of the gall bladder with gangrene (torsion).

From the Department of Surgery of the Loup City Clinic and the surgical service of the Sacred Heart Hospital.

COMMENT

Although torsion of the gall bladder must be quite rare, it should be considered in the differential diagnosis of any case of right upper quadrant abdominal pain. A history of repeated attacks which are relieved by lying down is quite comon. It can be readily seen that a gall bladder which hangs by a small pedicle would easily be subject to torsion. In children this would be a congenital anomaly. The more frequent occurrence of torsion in the elderly may be explained by the loss of fat and atrophy of tissue which may occur with advancing age, leaving the gall bladder hanging freely.

The present case is the youngest one reported in the English language as far as the writer has been able to ascertain.

REFERENCES

1. Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953.

2. Rawson, H. D.: Torsion of the Gall Bladder in a Child of 12 with a Review of the Literature, Australian & New Zealand J. Surg. **22**:315-317 (May) 1953.

News and Comment

ANNOUNCEMENTS

Annual Meeting of the American Academy for Cerebral Palsy.—The Annual Meeting of The American Academy for Cerebral Palsy will be held at the Claridge Hotel, in Memphis, Oct. 10, 11, and 12, 1955. The three-day meetings are open to members of the medical and allied professions who are interested in cerebral palsy.

Annual Cerebral Palsy Workshop.—The annual Cerebral Palsy Workshop will be conducted in the University Hospital School for Severely Handicapped Children, State University of Iowa, Iowa City, July 11-29, 1955. This workshop is designed for professional persons other than physicians who are engaged in work with children having cerebral palsy. The course content is broad in scope. Registration is limited. Interested persons should write to Dr. R. R. Rembolt, Director, University Hospital School for Severely Handicapped Children, Iowa City, for further information.

Coming Examinations to Be Held by The American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations according to the following schedules:

Detroit, April 1, 2, and 3, 1955

New York, June 10, 11, and 12, 1955

FAMILIAL INCIDENCE OF CRANIOSYNOSTOSIS

Report of Two Cases Occurring in One Family

LYLE A. FRENCH, M.D.
and
RALPH L. SUECHTING, M.D., Minneapolis

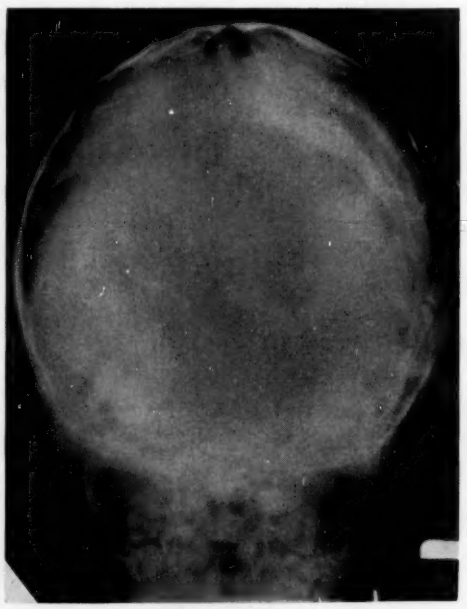
CRANIOSYNOSTOSIS, or premature closure of the cranial sutures, is a relatively unusual anomaly. During the last few years it has received reasonable clinical emphasis due principally to the writings of Ingraham, Alexander, and Matson [2] and others.[5] A very acceptable treatment has been devised, but the etiology is still unknown. Virchow,[7] in his original discussion, in 1851, suggested that the condition might result from inflammation of the meninges, and others have suggested that an intrauterine meningitis might be the cause. Metabolic disturbance from vitamin deficiency or glandular dysfunction have also been considered etiological factors. It has been felt by some that the anomaly is due to an inherent defect in the germ plasm, and there is no doubt that at least in certain instances the anomaly is familial and that it may be associated with other congenital defects. It has been reported to occur in siblings and even in succeeding generations in the same family. However, these reports are not numerous and in some instances not particularly well verified. It is the purpose of this report to present two cases, a brother and a sister, with craniosynostosis in order to emphasize this familial tendency. These cases are particularly interesting, since it was the mother who first suspected the lesion in the younger child and who was insistent upon having the child investigated for possible craniosynostosis.

From the Division of Neurosurgery, Department of Surgery, University of Minnesota.

REPORT OF CASES

CASE 1 (U. H. No. 740130).—This baby boy was admitted to the University Hospital, Minneapolis, on Jan. 22, 1944, at the age of 11 months, because of scaphocephaly and peculiar bobbing movements of his head. Roentgenograms revealed closure of the sagittal and coronal sutures. Both the posterior and the anterior fontanelle were closed (Fig. 1). On examination there was a questionable early bilateral optic atrophy. The head circumference measured 48 cm. On Jan. 26, 1944, under ether anesthesia, a strip of bone 1 cm. wide overlying the sagittal and coronal sutures was excised. The immediate postoperative convalescence was uneventful; the bobbing movements of his head dis-

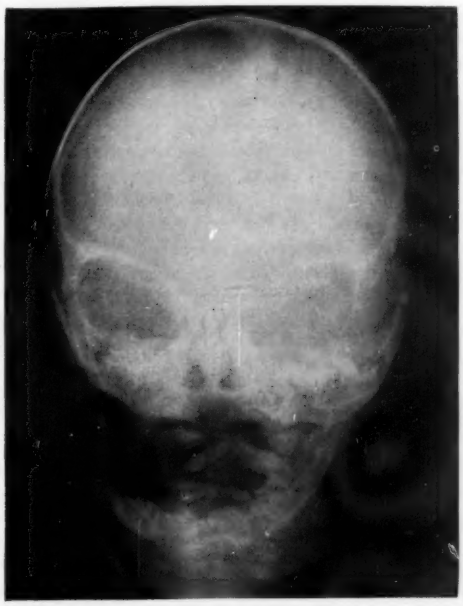
Fig. 1.—Photograph of roentgenogram of Case 1 showing premature closure of sagittal suture. The coronal and lambdoid sutures also were closed, but this is not visible in this projection.



appeared. However, roentgenograms obtained six months following the craniectomy revealed complete bony fusion along the suture line. On Dec. 11, 1946, under cyclopropane anesthesia, the coronal, sagittal, and lambdoid sutures were excised, and a layer of tantalum foil was placed around the margins of the parietal bones. The patient tolerated the procedure well, and his postoperative convalescence was uneventful. He subsequently has been followed in the outpatient department and is now 10 years old. Roentgenograms reveal no evidence of bony fusion along the line of excision. General physical examination when last seen, on June 15, 1954, revealed him to be a fairly well-developed well-nourished boy, who was obviously retarded mentally. Psychometric evaluation with Stanford-Binet Form M, Bender-Gestalt, and Good-enough Draw-A-Man tests were done. His measured I. Q. was 61. It was felt that he was working at a mentally defective level and that emotional factors did not overlay what was felt to be an organic etiology. He was responsive, genial, and maintained a satisfactory level of effort, even though recent memory seemed particularly impaired. It was felt that there had been progressive decline in intellectual capacity since the original psychometric evaluations in 1946. It is appreciated that at this earlier age the testing was less valid.

CASE 2 (U. H. No. 793658).—This patient is a sister of the boy presented in Case 1. She was admitted to the University Hospital on Aug. 16, 1948, at the age of 2 months. She had no symptoms referable to craniosynostosis, but, since this was the diagnosis made on her brother, the mother insisted on skull roentgenograms, which were taken at birth and at 6 weeks of age. These revealed progressive closure of both coronal and sagittal sutures (Fig. 2). Both anterior and posterior fontanelles were closed. Head circumference at this time was 47 cm. The head was scaphocephalic. On Aug. 18, 1948, under vinyl ether (Vinethene) anesthesia, a strip of bone 1 cm. wide along the sagittal and coronal sutures was excised. Polyethylene film was then laid around the free bone edge and sutured in place. Her postoperative convalescence was uneventful. Roentgenograms at the age of 6 months and 12 months revealed patent suture lines and symmetrical increase in the size of the entire head. Examination on June 15, 1954, when the child was 6 years of age, revealed a normal physical and mental development. Psychometric evaluation revealed her to be functioning at above normal level.

Fig. 2.—Photograph of roentgenogram of Case 2, showing premature closure of sagittal suture. This child was 6 weeks old at this time.



COMMENT

Reports in the literature of familial craniosynostosis include that by Bedell,[1] in 1917, who described the optic findings in three members in one family with craniosynostosis, and Sheldon,[4] in 1931, who reported the deformity present in a mother and three of her children. Skipper,[6] in 1934, described operative procedures in one of three siblings with craniosynostosis. Klein and Childe,[3] in 1936, reported the anomaly to be present in two members of one family. Simmons and Peyton [5] and Ingraham and co-workers [2] allude to the familial occurrence but present no specific cases.

It is believed that the two cases reported here emphasize the possibility of a familial incidence of craniosynostosis. There can be no doubt that the attention of the mother alerted us to the occurrence of the deformity in the second child. It is felt that its early recognition was of great importance in the ultimate successful result obtained.

SUMMARY

Two cases of craniosynostosis in siblings are reported. The possible familial occurrence of the deformity is emphasized.

REFERENCES

1. Bedell, A. J.: Oxycephalus: Report of 3 Cases with Operation in 1, J. A. M. A. **68**:1979, 1917.

2. Ingraham, F. D.; Alexander, E. J., Jr., and Matson, D. D.: Clinical Studies in Craniosynostosis: Analysis of 50 Cases and Description of a Method of Surgical Treatment, Surgery **24**:518, 1948.

3. Klein, O. L., and Childe, A. E.: Oxycephaly, with the Report of 2 Cases in a Brother and a Sister, Canad. M. A. J. **34**:379, 1936.

4. Sheldon, W.: Hereditary and Familial Oxycephaly, Proc. Roy. Soc. Med. **24**:574, 1931.

5. Simmons, D. R., and Peyton, W. T.: Premature Closure of the Cranial Sutures, J. Pediat. **31**:528, 1947.

6. Skipper, E.: Oxycephaly, with Report of 3 Cases in One Family, Quart. J. Med. **3**:579, 1934.

7. Virchow, R.: Über den Cretinismus namentlich in Franken und über pathologische Schädelformen, Verhandl. phys.-med. Gesellsch. **2**:230, 1851.

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in New Orleans, on March 4, 5, and 6, 1955.

Anderson, Esther Elizabeth, New Orleans.
Aponte, Joseph L., Santurce, P. R.
Bagnetto, Richard Lucas, New Orleans.
Ball, Albert L., Memphis.
Belnap, Wilford Dean, Fort Belvoir, Va.
Boles, Truett C., Jacksonville, Fla.
Britton, Howard A., San Antonio, Texas.
Cohen, Abe, Silver Springs, Md.
Delaney, Thomas Brendan, Natick, Mass.
Denley, Malcolm Lamar, Alexandria, La.
Denny, Ben Witcher, Dallas, Texas.
Easley, Curran S., Jr., La Grange, Ga.
Eckert, Philip A., Dayton, Ohio.
Ferrell, Elsie H., South Pasadena, Calif.
Fife, Robert Reed, Patrick Air Force Base, Fla.
Freede, Charles Louis, Oklahoma City.
Gans, Frederick A., Salina, Kan.
Gibson, Glenn G., Baton Rouge, La.
Graham, Mary Virginia, Tulsa, Okla.
Grimmett, Matthew Hill, Concord, N. C.
Harrison, Walton W., Jackson, Tenn.
Hart, Juanita Thacker, Bellaire, Texas.
Heersma, James Robert, Marshfield, Wis.
Hiatt, Wilks O., Jr., Pompano Beach, Fla.
Hoveman, Paul George, Pensacola, Fla.
Huelskamp, Margaret, San Jose, Calif.
Jacobs, Herbert J., New York.
Jenke, Albert, Waco, Texas.
Jones, John Paul, Macon, Ga.
Joseph, Sheldon William, San Antonio, Texas.
Kemberling, Sidney R., Tucson, Ariz.
Kennedy, Hughes, III, Birmingham, Ala.
Krafft, C. James, Dallas, Texas.
Lane, John G., Jr., Jacksonville, Fla.
Lovejoy, William Mathew, Memphis.
McNamara, Thomas W., Oxnard, Calif.
Mason, William Watson, Memphis.
Meek, Melton P., Lawton, Okla.
Molnar, Charles Joseph, Jr., San Diego, Calif.
Mullins, David Meredith, El Paso, Texas.
Nunn, William E., Los Gatos, Calif.
Nyman, Randall D., Fort Worth, Texas.
O'Brien, John C., St. Paul, Minn.
O'Hara, Bernard Francis, West Palm Beach, Fla.
Orr, William Wood, Macon, Ga.
Oven, Raney A., Tallahassee, Fla.
Richard, Robert Earl, Morgantown, W. Va.
Robinson, Jo Newell, Columbus, Miss.
Rosenblum, Louis, Corpus Christi, Texas.
Ruggieri, Bartholomew A., Rochester, Minn.
Sailors, Emma Lou, New Orleans.
Saltzman, Edward J., Camp Kilmer, N. J.
Schneider, Peter William, Camp Lejeune, N. C.
Segal, Jack, Memphis.
Sekul, Wallace Steve, Biloxi, Miss.
Simpson, Ellen, San Francisco.
Smith, James H., Miami Springs, Fla.
Smith, Richard Carlton, Oakland, Calif.
Snow, Robert Lee, Jr., Birmingham, Ala.
Spivey, Oscar S., Macon, Ga.
Spurlock, Mark Sutphin, Logan, W. Va.
Stammer, Dolores Virginia, Fresno, Calif.
Stands, Benjamin Osborn, Columbia, S. C.
Stewart, George Albert, Jr., Fort Worth, Texas.
Stratton, Emil F., Muskogee, Okla.
Tiblier, Sidney L., Jr., New Orleans.
Tuholski, James M., Memphis.
Tuttle, Arliss Hederick, Memphis.
Van Geyt, Virginia, New York.
Waring, William W., Jacksonville, Fla.
Wasserman, Charles Felix, New Orleans.
White, James William, Tulsa, Okla.
Wohltmann, Hulda J., St. Louis.

Abstracts from Current Literature

Acute Contagious Diseases

A Fatal Case of Poliomyelitis in a Newborn Infant Delivered by Cesarean Section Following Maternal Death Due to Poliomyelitis. Charles L. Swarts and Ervin F. Kercher, Pediatrics **14**:235 (Sept.) 1954.

A fatal case of poliomyelitis in a newborn is reported. The case is important, as the infant was delivered by Caesarean section within a few minutes after maternal death due to acute poliomyelitis. The same immunological strain of poliomyelitis virus was isolated from both infant and mother.

While positive proof is not offered, this case plus a review of the literature offers strong evidence that transplacental transfer of the poliomyelitis virus can occur.

From the Authors' Summary.

Is the Absence of Pharyngeal Tonsils a Predisposing Factor to the Bulbar Forms of Poliomyelitis. M. Pestel, Presse méd. Supp. 64, p. 1328, Oct. 2, 1954.

Why do only a few subjects among those affected by poliomyelitis virus in epidemic periods react by nervous involvement?

Why, in this localization, is the spinal cord most commonly damaged, either in a bulbospinal form or in a pure bulbar form? Both questions have not so far been answered, and the problem remains unsolved. A series of epidemological inquiries, as recently carried out in the most scientific manner and as based on a large number of statistical records, have led to the conclusion that the highest incidence of the upper bulbar forms of poliomyelitis was encountered in those subjects previously tonsillectomized. In the course of a poliomyelitis epidemic, the absence of pharyngeal tonsils would increase by about four times the risk of upper bulbar involvement among patients affected by the virus.

The observations, being concurrent with the increase in incidence of the upper locations of the virus as statistically established, should be the object of further researches, so that there might be defined the degree of connection between the two phenomena.

From the Author's Summary.

The Eliminations of 17-Ketosteroids in Scarlet Fever and Measles. A. Macciotta, Ann. ital. pediat. **7**:233 (Aug.) 1954.

After a short review, the author thinks that it is not useless to seek, even in isolated cases, the urinary 17-ketosteroids, at least in particular conditions.

He relates the data concerning two groups of patients (11 with scarlet fever and 11 with measles) in whom the urinary ketosteroids were estimated in the acute stage and remittent stage of the morbid process. The observation showed in scarlet fever a prevailing increase of elimination in the first state and afterwards a decrease and return to normality in most cases.

In measles (acute stage) the tendency to increase was, on the contrary, less marked.

After discussing the results obtained, the author points out the practical importance of these remarks.

From the Author's Summary.

Changes in the Spinal Fluid Occurring in the Course of Heine-Medin Disease. B. Rondinini and M. Malossi, Clin. pediat. **6**:375 (May) 1954.

Data are presented as to the cell counts and the albumin content of the spinal fluids from 227 patients with poliomyelitis during the epidemic of 1953 in Bologna.

In the early stages of the disease, the polymorphonuclear cell counts are high; they fall as the disease progresses.

In most cases the cell counts do not parallel the albumin content. The severity of the disease does not parallel the cell counts or the albumin content.

The albumin content is usually highest at about 20 days from the onset of the disease.

Higgins, Boston.

EPIDEMIOLOGICAL ASPECTS IN POLIOMYELITIS. A. MALLARDI, Lattante **25**:352 (June) 1954.

Three children in one family, ages 9 months, 2 years, and 3 years, developed poliomyelitis with paralysis, with an interval of five days between onsets. A cousin had had the disease two years previously, and a grandmother when a child.

In another family twins developed poliomyelitis simultaneously.

In neither of these cases were there other cases in the neighborhood.

The suggestion is offered that there may be a constitutional predisposition to paralysis in poliomyelitis.

HIGGINS, Boston.

TREATMENT OF PERTUSSIS WITH ANTIBIOTICS. B. DE RUDDER and H. VETTERMANN, Deutsche med. Wchnschr. **79**:1317 (Sept. 3) 1954.

Three hundred fourteen infants admitted to the hospital with pertussis during the first year of life were treated with antibiotics—streptomycin, chloramphenicol, and lately, chlortetracycline (Aureomycin), and the results compared with 263 pertussis cases admitted before antibiotics were available. The incidence of pneumonia after admission was reduced to about one-fifth, and the morality due to pneumonia to one-third. In infants with pneumonia on admission, the mortality was reduced to only one-half. The mortality of admission without pneumonia dropper to one-sixteenth, and the total mortality to about one-fourth.

AMBERG, Rochester, Minn.

PROBLEMS OF SCARLET FEVER, EXAMINATIONS DURING AN EPIDEMIC IN BERLIN: PROPHYLAXIS. HEINRICH WIESENER, Deutsche med. Wchnschr. **79**:1320 (Sept. 3) 1954.

Large-scale vaccinations with combined diphtheria, scarlet fever, pertussis, or diphtheria-scarlet fever vaccine were carried out in West Berlin; of these, 80% to 90% were done in two-year- and six-year-old children. The results over-all are tabulated; of 97,127 nonvaccinated children, 7336 acquired scarlet fever; of 25,028 vaccinated children, 598. The protection diminishes in the third year after vaccination. Some good prophylactic results are described with penicillin. Vaccination against scarlet fever is recommended under certain conditions.

AMBERG, Rochester, Minn.

Acute Infectious Diseases

AN EVALUATION OF CHLORAMPHENICOL THERAPY IN TYPHOID FEVER IN CHILDREN. ABRAHAM FRIEDMAN, Pediatrics **14**:28 (July) 1954.

In the light of the author's experience with chloramphenicol therapy of typhoid fever in 122 children, the following conclusions appear to be valid.

Prolonged chloramphenicol therapy is unnecessary, undesirable, and sometimes even harmful. The course of therapy should be limited to the period of fever and continued for just one or two days after the temperature has become normal. This view is based upon the following considerations: 1. The finding that relapses were just as frequent on longer courses as on shorter ones. 2. Prolonged courses of chloramphenicol expose the patient more intensely to the hazard of severe and sometimes fatal gastrointestinal disturbances. 3. Prolonged courses may expose the patient more seriously to severe and sometimes fatal bone marrow depressions. 4. This conclusion is of special importance where the availability of the drug and the expense involved are factors to be taken carefully into consideration.

Except in hypertoxic forms of typhoid, chloramphenicol therapy should be instituted as early as possible and should not be delayed for any reason. This view is based upon the following considerations: 1. On the one hand, when chloramphenicol is started early, during the first week of illness, the relapse rate is higher in comparison to the relapse rate when therapy is started later. 2. On the other hand, complications and mortality rates are considerably higher when therapy is postponed to the second week or later. 3. Weighing these two hazards against each other, it appears that the latter outweighs the former and that it would certainly be wiser to take the risk of a relapse than of a severe complication or a fatality, and therefore therapy should be started in every case as early as diagnostic considerations permit.

In hypertoxic forms of typhoid, chloramphenicol therapy should be withheld at the beginning, trying supportive therapy, including blood transfusions. Later chloramphenicol may be started but with small doses only, perhaps 12.5 mg/kg/day. If no deterioration in the general condition

takes place it may then be increased, three to four days later, to 25 mg/kg/day, and three to four days later again, to 50 mg/kg/day, provided the general condition of the patient does not deteriorate.

If in spite of special care in instituting chloramphenicol therapy in hypertoxic forms of typhoid an intestinal perforation-like syndrome develops, chloramphenicol therapy should be stopped immediately and general supportive measures instituted as soon as possible. The same applies when the intestinal perforation-like syndrome develops suddenly in a patient not previously severely toxic.

Gastrointestinal disturbances during chloramphenicol therapy should be taken seriously, and any degree of severity in such disturbances warrants the immediate cessation of chloramphenicol with the immediate institution of corrective measures to combat the electrolyte disturbances which might have resulted.

FROM THE AUTHOR'S SUMMARY.

POST-TYPHOID ENCEPHALOPATHIES IN CHILDREN. M. SCHACHTER, Ann. pædiat. **183**:58 (July) 1954.

The author describes the neurological complications of the typhoid infection in adults and children and gives also a general review of the neuromental sequelae of this infection. He thinks that relatively few contributions mention such sequelae (in children and adults), and he presents 10 personal cases of children and young adolescents who exhibit neuromental manifestations of typhoid origin.

FROM THE AUTHOR'S SUMMARY.

A NEW CASE OF THE SO-CALLED CAT SCRATCH DISEASE. D. BULLIO and A. FORTINA, Minerva pediat. **6**:349 (May 15) 1954.

A 7-year-old boy, one month after being scratched by a cat, developed a swelling in the right axilla; it was the size of a pigeon's egg and not painful. A gland was removed; the central portion was found to be necrotic and surrounded by lymphoreticular reaction. A skin test, using Debre's antigen, proved to be positive. Penicillin proved to be of no therapeutic value, but chlortetracycline (Aureomycin) and vitamin B complex led to rapid regression of the glandular swelling.

HIGGINS, Boston.

LOCALIZED OSTEITIS IN CHILDREN WITH BRUCELLA INFECTIONS. M. VERROTTI and D. FORTE, Pediatria **62**:80 (Jan.) 1954.

Two children developed an osteitis of the femur in the course of a Brucella infection. In an 8-year-old child, the involvement was of the greater trochanter of the femur; there was no longer any activity after three months, and complete healing after six months. In a 2-year-old child, the involvement was of the epiphysis and diaphysis of the head of the femur and resulted in complete destruction of this area and marked functional impairment.

HIGGINS, Boston.

THE PATHOGENESIS OF ANEMIA IN TYPHOID FEVER: BONE MARROW STUDIES. A. CROSCA and R. DE LUCA, Pediatria **62**:164 (March) 1954.

Bone marrow studies were made on eight children with typhoid fever. The cells of the granulocytic series were found in greater proportion than in the marrow of normal children, except that the eosinophilic granulocytes were fewer. The low granulocyte counts in the blood of typhoid fever patients must be due to a lowering of the rate of migration of the cells from the marrow to the blood stream, or to destruction of the granulocytes in the blood stream by toxins. The erythroblastic cells in the marrow were found to be slow in maturing; anemia in typhoid fever would appear to be due to the destruction of red cells in the blood happening at a more rapid rate than the production of new cells.

HIGGINS, Boston.

TYPICAL AND RUDIMENTARY FORMS OF BORNHOLM DISEASE (INSTITUTIONAL EPIDEMIC). A. WINDORFER and H. SCHRICKER, Med. Klin. **49**:1069 (July 2) 1954.

In a home for children housing 41 inmates, four typical cases of Bornholm disease occurred. In six cases, the disease was rudimentary, including two with a herpes angina. Two adults of the home had typical attacks; in two others the disease was atypical. A brother of one of the inmates

was infected and infected an uncle. The typical and rudimentary forms are illustrated by case histories. The diagnosis rested on epidemiological connection. No virus studies are reported.

AMBERG, Rochester, Minn.

BACTERIOLOGICAL STUDY IN CHILDREN WITH MUCOVISCIDOSIS. M. R. H. STOPPEIMAN, Maandschr. kindergeneesk. **22**:318 (Sept.) 1954.

Chlortetracycline (Aureomycin) is to be preferred above oxytetracycline (Terramycin) in the treatment of children with mucoviscidosis from a bacteriological point of view. This conclusion is made considering the differences in the predominance of pyogenic Staphylococcus and in the incidence of Pseudomonas and Proteus in the nasopharynx in the chlortetracycline- and in the oxytetracycline-treated patients.

The changes in the flora of the stool in the patients with mucoviscidosis who received continuously antibiotic therapy are not so extensive that disturbances and inflammatory processes in the intestines are likely to occur.

Although yeasts were present in 10% to 12% of the nasopharyngeal swabs and in 18.5% of the rectal swabs, this micro-organism was not found in pure culture and did not predominate in any of the cases.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

TOTAL BODY CHLORIDE IN TUBERCULOUS MENINGITIS. DONALD C. CHEEK, Pediatrics **14**:87 (Aug.) 1954.

Seven children with tuberculous meningitis have been studied. In the absence of fluid restriction and vomiting, hypotonic expansion of the extracellular fluid has been revealed. This draws attention to an alteration in water excretion. Metabolic alkalosis yields evidence of cell potassium depletion. The serum chloride is no indication as to the status of total body chloride.

FROM THE AUTHOR'S SUMMARY.

RESULTS OF TREATMENT IN SOME FORMS OF TUBERCULOSIS IN CHILDREN WITH I. A. I. A. GENTILI and A. PACI, Riv. clin. pediat. **53**:385 (May) 1954.

A report is submitted on the results which were obtained by employing I. A. I. in the treatment of 62 cases of tuberculosis in childhood. The forms which have been greatly influenced by the treatment are as following: tuberculous meningitis, disseminated bronchopneumonia with or without cavities, pneumonic infiltrations with secondary adenopathy in the parenchymal component, hilomediastinal adenopathies followed by epituberculous-like perifocal reactions in the exudative component, and serosities.

Poor results have been obtained in the hilar adenopathies, accompanied or not by parahilar infiltrations.

The authors discuss indications and modalities of the I. A. I. treatment, concluding that the new drug, even if useful, does not essentially change the course of the usual forms of ganglio-penumonic tuberculosis in childhood.

FROM THE AUTHORS' SUMMARY.

CORTISONE IN TUBERCULOUS MENINGITIS. PROSPERI PAOLO and ROSSI ROANO, Riv. clin. pediat. **53**:413 (May) 1954.

Thirty patients affected by tuberculous meningitis or its after-effects were treated with small doses of cortisone. In 5 cases such treatment was used in order to correct the ocular consequences; in the remaining 25 cases cortisone was administered with the aim to dissolve or to prevent blocks in the spinal fluid or to attempt to remove paresis, deafness, etc., caused by the disease. The treatment, performed only by intraspinal puncture in some cases and by general treatment in the others, led to more or less successful results; in 16 of 25 cases (64%) the blocks were removed. The author's own experience suggests that cortisone displays its effectiveness during the course of tuberculous meningitis in the following ways: (*a*) decrease of spinal fluid block frequency; (*b*) decrease of cerebral spinal fluid protein level; (*c*) shortening of the duration of the disease; (*d*) a better prognosis. No harm has been noted due to cortisone.

FROM THE AUTHORS' SUMMARY.

NEUROLOGIC COMPLICATIONS IN TUBERCULOUS MENINGITIS. MARIO VENEGAS YANEZ, Rev. chilena pediat. **25**:219 (May) 1954.

Seven hundred patients with tuberculous meningitis treated by Prof. R. Debré and co-workers are analyzed within the years 1947-1953. The study is centered in the neurologic disorders appearing during the treatment of the disease; in relation to this it is interesting to point out the following things.

Among the most important neurologic disorders are ocular paralysis, convulsions, hemiplegia, posterior cisternitis, blindness, and spinal forms. These complications aggravate the vital prognosis of the tuberculous meningitis.

The tuberculous meningitis treated has shown a syndrome very rarely observed before and during the chronic evolution of the meningoencephalitic lesions. Among the neurologic disturbances of the chronic form the following should be pointed out: the Parkinsonian syndromes, the forms with rigidity of decerebration, the ones with contractures in flexion, and the ones with hydrocephalus. The functional and vital prognosis of these complications is bad, and the ones with the worst prognosis are those of rigidity of decerebration and those with hydrocephalus. From the functional point of view the most serious complication is blindness, which in certain cases can be cured by means of an opportune operation in the optochiasmatic region. At the same time, from the vital point of view, the most severe complications are the meningeal hemorrhages.

The most important indications for neurosurgical treatment are intracranial hypertension, hydrocephalus, blindness, and intracranial hemorrhages. FROM THE AUTHOR'S SUMMARY.

INTRACRANIAL CALCIFICATIONS IN TUBERCULOUS MENINGITIS. MARIANO LATORRE, JORGE HOWARD, and RODOLFO MERELLO, Rev. chilena pediat. **25**:266 (June) 1954.

In a series of 31 cases in children recovered from tuberculous meningitis and which have been observed from two to six years, 11 have shown intracranial calcification demonstrable under x-ray. In all of them the calcifications were in the posterior or middle fossae. The calcifications in the middle fossae keep a strict anatomical relationship with the basal cisterns; those of the posterior fossae with the cisterna ambiens and the cisterna magna.

For better study the material was divided into groups, one of eight cases whose length of observation varied between 24 and 26 months and of which only one had a calcification. In the other group, of 23 cases, whose periods of observation varied from three years and two months to six years, 10 presented calcifications seen under x-ray. No relationship was found between the calcifications and the sequelae. Lastly, the pathology of these lesions is analyzed.

FROM THE AUTHORS' SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

AGENESIS OF THE SPLEEN, HEART AND VESSEL MALFORMATIONS, AND SITUS INVERSUS PARTIALIS: A CHARACTERISTIC SYNDROME. J. BAUMANN, Helvet paediat. acta **9**:199 (June) 1954.

The observations of agenesia of the spleen, severe heart and vessel malformations (cor biloculare), partial situs inversus, and abnormal lobation of the lungs have been reported in two children aged one 1½ hours and 3 days. It is concerned with a typical symptom complex of simultaneous developmental disturbances, the etiology of which is not yet known.

FROM THE AUTHOR'S SUMMARY.

STRIDOR IN ANOMALIES OF THE AORTA. C. E. VAN DER HOOG, Maandschr. kindergeneesk. **22**:222 (July) 1954.

The author reviews the different causes of stridor, with special reference to aortic anomalies. Recurrent pulmonary infection may be the only symptom, as is demonstrated by the histories of two patients with a rather uncommon abnormality, a right aortic arch with right descending aorta and left subclavian artery running behind the esophagus, while the left subclavian and pulmonary arteries were connected by an obliterated ductus Botalli compressing the trachea and esophagus. The operative results were disappointing.

FROM THE AUTHOR'S SUMMARY.

WOLFF-PARKINSON-WHITE SYNDROME IN AN INFANT FOUR WEEKS OLD. H. VAN DONK, Maandschr. kindergeneesk. **22**:238 (July) 1954.

The author gives a case report of a 4-week-old baby with paroxysmal tachycardia and the Wolff-Parkinson-White syndrome, treated with digitalis, quinidine sulphate, and procaine amide hydrochloride.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat, and Ear

CAUSES OF DEAFNESS IN YOUNG CHILDREN. EDMUND P. FOWLER JR., A. M. A. Arch. Otolaryng. **59**:476 (April) 1954.

Of 270 deaf children under 10 years of age, in 81, or 30%, the deafness was due to prenatal causes (10 preconceptional, 50 during pregnancy, and 21 during labor). One hundred eighty-nine out of 270 children (70%) had deafness due to postnatal causes (45 from otitis media, 11 from miscellaneous causes). The causes of deafness are more thoroughly investigated now so that the catch-basket "congenital" is seldom used. There is need of places and personnel to train these children properly.

KIMBALL, Evanston, Ill.

EXOGENOUS FOREIGN BODIES OF THE EXTERNAL AUDITORY CANAL, NASAL CAVITY, AND ESOPHAGUS. J. C. PEELE, A. M. A. Arch. Otolaryng. **59**:672 (June) 1954.

Foreign bodies of the external auditory canal, nasal cavity, and esophagus are not common and seldom produce symptoms if removed promptly. Most can be removed without a general anesthesia, but skill is imperative to prevent further injury. A foul odor of undetermined origin may be the initial symptom of a nasal foreign body.

KIMBALL, Evanston, Ill.

TONSILLECTOMY AND ADENOIDECTOMY. JOSEPH A. JOHNSTON and THOMAS W. WATKINS, J. Pediat. **44**:127 (Feb.) 1954.

The tonsil and adenoid problem is not a simple one. Cold statistics on the value of tonsillectomy and adenoidectomy can be misleading. In this report, Johnston and Watkins take into account the normal involution of this tissue. They recognize the importance of allergy and they point out the value of chemotherapy and antibiotics. They agree that the privilege of operation may be abused but think that we may sometimes be too conservative. In selected cases, they say, removal of tonsils and adenoids may be helpful.

In their study of 598 cases, removal of tonsils and adenoids reduced a significant number of frequent respiratory infections and ear infections and cases of abdominal pain referrable to chronic throat infection. Recurrent bronchitis was improved most in children over 4 years of age. With sinus infection and with asthma, the results were equivocal. However, the authors state that it is illogical to try to desensitize the asthmatic patient with bacterial vaccines in the presence of infected tonsils in a child over 8 years whose attacks are always precpitated by infection.

In properly selected cases, removal of tonsils and adenoids may improve the appetite and nutritional state, may help to prevent recurrent vomiting, and may be indicated in cases of infectious arthritis.

The authors stress that the decision for surgery must be arrived at after sufficient observation has excluded other causes for the presenting complaint.

MACDONALD, Pittsburgh.

A SUMMER RESIDENTIAL PROGRAM IN HEARING EDUCATION. J. C. KELLY, J. Speech & Hearing Disorders **19**:17 (March) 1954.

The author gives a description of 40 children in attendance at the University of Illinois summer residential program: 22 hard of hearing, 13 cleft palate, and 5 cerebral palsy, in an age group of 10 to 17 years. An all-day program in hearing education demands a structure that will sustain the interest of the child as well as provide a satisfactory gain in the skills necessary for improved communciation. Group methods in hearing education as described appear to be quite satisfactory in producing measured gains in performance. Theatre and music therapy as complementary activities in such an educational program appear promising. A rotating plan of talker-listener group education was utilized with significant improvement.

PALMER, Wichita, Kan.

THE RATING OF DEFECTIVE SPEECH BY TRAINED AND UNTRAINED OBSERVERS. ELINOR HORWITZ PERRIN, J. Speech & Hearing Disorders **19**:48 (March) 1954.

Voices of seven children of varying degrees of articulatory difficulty were arranged on magnetic tape for paired comparisons and played before one group of judges with no training in speech therapy and one with much training. The trained and untrained judges did not differ significantly in their evaluations of severity. Both groups showed a significant amount of agreement within their respective groups in rankings, with better agreement among the untrained group. Both groups showed many inconsistencies. The correlation coefficient between the number of sounds misarticulated and the judges' rankings was significant at the 4% level for untrained judges and better than the 1% level for trained judges.

PALMER, Wichita, Kan.

EMOTIONAL INVOLVEMENTS IN SOME FORMS OF MUTISM. HILDE M. ADAMS and PHILIP J. GLASNER, J. Speech & Hearing Disorders **19**:59 (March) 1954.

A small number of children who do not speak show no evidence of organic involvement and are resistant to intensive speech therapy. Four nonrelated cases reported by the authors came from severely disturbed home situations lacking any semblance of emotional and physical security. The fathers were alcoholics, and all of the children were extremely afraid of them. All utilized pantomime and sign language in attempts to communicate and under great stress were reported to utter words or short unorganized sentences. Very little success was attained in an attempt to initiate oral communication. The authors believe that therapy should be on a psychotherapeutic level.

PALMER, Wichita, Kan.

AN ANALYSIS OF AN EXCEPTIONAL CASE OF RETARDED SPEECH. GEORGE O. EGLAND, J. Speech & Hearing Disorders **19**:239 (June) 1954.

This is a presentation of the techniques used to produce speech in a case of serious speech retardation with loss of vision and moderately severe cerebral palsy. Since babbling was missing in this case, the main attack was on stimulating babbling.

PALMER, Wichita, Kan.

RECENT OBSERVATIONS ON THE USE OF NASOPHARYNGEAL IRRADIATION FOR THE CONTROL OF HEARING IMPAIRMENT IN CHILDREN. JOHN E. BORDLEY, South. M. J. **47**:246 (March) 1954.

The author presents a preliminary report on a study of 5000 children. Five hundred of these were selected for intranasal treatment with anhydrous radium sulfate applicators. One-half of this group were used as controls, the applicator being used without radium. The physicians giving treatment and following the children did not know which were the real and which were the control applicators. It was noted that a marked reduction in lymphoid tissue takes place following irradiation and that severe conductive type hearing loss of fluctuating type is improved by this technique. There was no untoward effect noted from the treatment employed.

LOGAN, Rochester, Minn.

CONGENITAL STRIDOR AND MALFORMATIONS OF THE TRACHEA. W. HIRSCH, M. LOEWENTHAL, and S. SWIRSKY, Ann. pædiat. **182**:1 (Jan.) 1954.

Three cases of obstructive laryngotracheal conditions (inspirational and expirational congenital stridor) are presented in children 4 months, 9 months, and 2.9 years old. In the first two, the postmortem examination showed a defect in the formation of the trachea above the bifurcation. In the third, which developed normally later on, the same congenital malformation of the cartilagenous rings of the trachea could be assumed on the basis of x-rays and direct tracheoscopy. The relation between the anatomical and the clinical signs is discussed.

FROM THE AUTHORS' SUMMARY.

OCCURRENCE OF INCLUSION BODIES, SUPPOSEDLY ON A VIRAL BASIS, IN THE EPITHELIUM OF PHARYNGEAL MUCOSA. W. GARVELMANN, Ztschr. Kinderh. **71**:268, 1954.

Examinations of the epithelium of the pharyngeal mucosa of infants examined at random proved the occurrence of inclusion bodies in almost all children. This makes their diagnostic significance for virus pneumonia in premature infants doubtful.

GLASER, Jerusalem.

Diseases of Lungs, Pleura, and Mediastinum

TREATMENT OF BACTERIAL PNEUMONIA WITH ERYTHROMYCIN. WAYNE S. WADDINGTON, FRANCIS M. MAPLE, and WILLIAM M. M. KIRBY, A. M. A. Arch. Int. Med. **93**:556 (April) 1954.

The authors summarize their experience in treating 75 patients with proved bacterial pneumonia with erythromycin. The results were comparable to those obtained with the broad-spectrum antibiotics or with penicillin. Side-effects were neglible and consisted of mild nausea and vomiting. It is concluded that erythromycin is highly effective in the treatment of pneumonia due to Gram-positive bacteria.

JONES, Chicago.

SPIROMETRIC ANALYSIS OF LUNG FUNCTION FOLLOWING PULMONARY RESECTION IN CHILDHOOD. J. A. TURNER, Pediatrics **13**:17 (Jan.) 1954.

A group of 40 persons who underwent pulmonary resection in childhood were studied by means of spirometric tracings. The time interval between operation and testing varied from 3 months to 19 years. The ages at operation ranged from 3 to 15 years.

No significant disturbance of resting ventilation, oxygen consumption, or average tidal air was found. Reduction in vital capacity corresponded to the extent of resection performed and was more marked in those instances in which bilateral resection was necessary. It was noted that reduction in vital capacity was more evident in the inspiratory phase in all instances except those suspected of having continuing pulmonary disease. In these persons the reduction in vital capacity was more marked in the expiratory reserve phase.

Maximum voluntary ventilatory capacity reduction was likewise compared to extent of surgical resection and showed a correlation similar to that of vital capacity. Evidences of pulmonary emphysema were more apparent in those cases whose maximum breathing capacity was markedly reduced. In all but one instance breathing reserve figures were within the normal range.

Although children tolerate pulmonary surgery extremely well, the age at operation is not the significant factor in the degree of resultant pulmonary function. The important factors are those of extent of pulmonary resection and consequent pulmonary emphysema.

FROM THE AUTHOR'S SUMMARY.

FACTORS INVOLVED IN PRODUCTION OF ALVEOLAR RUPTURE WITH MECHANICAL AIDS TO RESPIRATION. JAMES L. WILSON, Pediatrics **13**:146 (Feb.) 1954.

The amount of alveolar rupture and hemorrhage resulting from artificial respiration is dependent not only upon the degree of pressure and the time it is applied but also on the proportion of total lung volume that is expansible. The danger of such rupture is greater for a given pressure change, the greater the amount of unexpansible lung. The amount of atelectasis, pulmonary congestion, or obstruction that prevents expansion of lung is clinically not quantitatively measurable, so that no exact rule for time and pressures can be established that will be completely safe.

FROM THE AUTHOR'S SUMMARY.

AN INQUIRY INTO THE ETIOLOGY OF ACUTE BRONCHIOLITIS OF INFANTS. SARAH H. WOOD, G. JOHN BUDDINGH, and BENJAMIN F. ABBERGER JR., Pediatrics **13**:363 (April) 1954.

Tracheal aspirates and nasopharyngeal swabs obtained from 51 infants under 2 years of age with acute bronchiolitis were subjected to a careful bacteriologic study. The cases in this series were encountered during the 13-month period from Nov. 1, 1951, to Dec. 1, 1952.

Hemophilus influenzae was recovered from 36 of the 51 infants. Of these, 26 proved to be H. influenzae Type A and 6 proved to H. influenzae Type B. The four remaining were rough untypable strains.

An increase in type-specific antibody measured by a slide agglutination technique and by the quellung reaction could be demonstrated in 46 infants. No increase in antibody titer could be demonstrated in five. An increase in antibody titer to H. influenzae Type A was demonstrated in 37 and to H. influenzae Type B in 9 of the series.

Combined bacteriologic and serologic evidence indicating that H. influenzae Type A was involved in the infectious process was obtained in 26 cases. An increase in antibody titer to Type A only was demonstrated in 11 others. In two from whom rough nontypable strains were

isolated, an increase in titer to Type A was demonstrated. Evidence for infection with Type A was thus obtained in 37 of the 51 infants. From two infants, H. influenzae Type A was recovered, but no increase in antibody titer could be demonstrated.

Combined bacteriologic and serologic evidence for infection with H. influenzae Type B was obtained in five infants. An increase in titer to Type B was demonstrated in two others. A titer increase to Type B was demonstrated in two more from whom rough untypable strains were isolated. Evidence for infection with Type B was thus obtained in 9 of the 51 infants. H. influenzae Type B without evidence of titer increase was obtained in one.

No H. influenzae was isolated nor could an increase in antibody titer be demonstrated in the remaining two infants of the series.

Cold hemagglutinin reactions were negative in 36 pairs of sera tested. No increase in antihemagglutinating titer to influenzae virus A or B could be detected in 46 paired sera. A fourfold, but not greater, increase in antihemagglutination titer to influenzae virus C was detected in five patients of the series.

Reversion of rough untypable H. influenzae to smooth specifically typable strains was achieved by culturing the micro-organisms in chick embryos infected with influenza virus Type A.

It is postulated that H. influenzae Types A and B must be strongly considered as participating in the pathogenesis of acute bronchiolitis of early infancy. Whether other bacterial or viral agents alone or a combination of bacteria on viruses can be implicated in the etiology of this disease must be determined by further investigation.

FROM THE AUTHORS' SUMMARY.

EMPHYEMA. S. M. MERCHANT, Indian J. Child Health **3**:7 (Jan.) 1954.

Contrary to the trend in the current literature, emphyema has increased in incidence in Bombay. The very marked rise has suggested improper and inadequate dosage of sulfonanides and antibiotics.

Ten cases were studied in detail. Two died, one within 48 hours of admission, the other being tuberculous. Five cases treated with aspiration and instillation of penicillin recovered completely. One other required surgical treatment, and a tuberculous empyema improved slowly on chemotherapy.

McGUIGAN, Evanston, Ill.

A NEW SERODIAGNOSTIC METHOD WITH REGARD TO THE INTERSTITIAL PLASMA-CELLULAR PNEUMONIA OF YOUNG INFANTS AND PREMATURES. OSKAR VIVELL, Deutsche med. Wchnschr. **79**:358 (Feb. 26) 1954.

An antigen was prepared from a piece of lung from an infant which died from interstitial pneumonia. It contained numerous pneumocysts. The method of preparation is described. This antigen was used for complement fixation reaction. With this antigen antibodies could be demonstrated in the serums of nine typical cases of interstitial plasma-cellular pneumonia. The serum of 24 infants without pulmonal disease never gave a positive reaction, neither did that of 11 young children with other lung involvements, with the exception of 1 where a titer of 1:4 was found.

AMBERG, Rochester, Minn.

CONSTITUTIONAL STIGMATA OF ASTHMA IN CHILDREN. G. J. HUET, Maandschr. kindergeneesk. **22**:73 (March) 1954.

Clinical observation of 187 asthmatic children during 6-19 months showed that asthma occurs in two different forms: (*a*) 82 children were and remained quite free from attacks after a change of environment ("mild form"), (*b*) 105 children continued to suffer from attacks of asthma just as they did before admission ("severe form"). There proved to be a correlation between the frequency of the asthma attacks, the physical signs, and the pattern of pulmonary function, which may be due to the fact that all three are equally dependent on the degree of eosinophilic infiltration of the bronchiolar mucosa.

As the rate of the residual air of these children usually decreased and the rate of vital capacity increased with growth, it may be that the condition of asthmatic children in general improves automatically as they grow older. This holds principally for the milder forms of asthma. A further investigation was made as to the frequency of constitutional signs among the cases of mild asthma and those of severe asthma. It proved that a positive family history, eczema, and persistent skin lesions are more frequent in the latter. Furthermore, severe asthma

usually starts at an earlier age than the milder type. For these reasons it seems that severe asthma is constitutional in nature, while the milder form seems to be independent of this factor.

The importance of careful discrimination between these two types of asthma is discussed.

FROM THE AUTHOR'S SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

IMPERFORATE ANUS WITH RECTO-VESICAL, -URETHRAL -VAGINAL AND -PERINEAL FISTULA. WILLIS J. POTTS, WILLIAM L. RIKER, and ARTHUR DEBOER, Ann. Surg. **140**:381 (Sept.) 1954.

Fifty-one patients with imperforate anus complicated by communication with the genitourinary tract or perineum have been operated upon during the past seven years by the authors.

These patients with rectovesical or rectourethral fistula will develop symptoms of bowel obstruction soon after birth. If the diagnosis is made promptly, they are operated on during the first day of life.

The article is well illustrated, and operative treatment is given in detail. Preoperative and postoperative care is discussed.

BANTIN, Omaha, Nebr.

EFFECT OF ANTIBIOTIC THERAPY ON MUCOVISCIDOSIS: A BACTERIOLOGIC STUDY. MARIE R. H. STOPPELMAN and HARRY SHWACHMAN, New England J. Med. **251**:759 (Nov. 4) 1954.

The aerobic flora of the nasopharynx and stools were studied in 140 patients with mucoviscidosis who had received antibiotic therapy continuously for periods of as long as six years. The relation of such prolonged therapy to changes in bacterial flora and the occurence of antibiotic resistance are discussed.

These observations confirm the previous conclusion that despite the appearance of antibiotic resistance in the nasopharyngeal flora of these patients satisfactory clinical response may still be obtained.

WHEELOCK, Denver.

ILEO-ILEAL INTUSSUSCEPTION IN A CHILD. STUART P. BARDEN, Radiology **63**:542, 1954.

An ileoileal intussusception following Henoch's purpura, originating in a Meckel's diverticulum, is reported in a child 2 years of age. Because of extensive gangrene, 3 ft. (91.4 cm.) of ileum had to be removed. The convalescence was complicated by a pelvic abscess and signs of intermittent apparently incomplete intestinal obstruction. The child was still living two months after surgery.

ANSPACH, Riverside, Ill.

HYPOPLASIA OF THE PANCREAS. E. FREUDENBERG, Ann. pædiat. **183**:321 (Dec.) 1954.

The modern conception of fibrocystic disease of the pancreas as a "mucosis" or "mucoviscidosis" makes changes in the respiratory system obligatory. Patients who for years only present the syndrome of celiac disease do not belong to the entity of fibrocystic disease of the pancreas.

Three cases are described in whom those changes were constantly missing but who had no or very scanty enzymes present in their duodenal juice and a history of chronic dyspepsia.

A comparison with cases of pancreatic hypoplasia, verified anatomically, showed only one peculiarity; our cases had pathological blood sugar curves after double doses of glucose, an observation not previously made by other authors.

It appears to be striking that the retardation of general development and growth in our cases was slighter than that usually seen in fibrocystic disease. On the other hand, cases were found in the literature with severe retardation in pancreatic hypoplasia. Apparently the degree of hypoplasia was responsible.

The clinical diagnosis of a cystic pancreas seems to be possible only when signs of cystic lungs or kidneys are present.

FROM THE AUTHOR'S SUMMARY.

SURGICAL TREATMENT OF HIRSCHSPRUNG'S DISEASE. JULIO MONEREO, Acta pediat. españ. **12**:525 (June) 1954.

The author reviews the literature on the theories of cause of Hirschsprung's disease and treatments prior to the use of surgery.

The method used by Dr. Monereo is a three-stage operation which has been quite successful in eliminating the symptoms of the disease. Whether or not there is an absence of the plexus of Auerbach, the type of operation described has been effective.

Only cases of true Hirschsprung's disease should be subjected to this procedure. It should be proved radiologically and by endoscopic examination that there is stenosis of the rectum with dilatation of the sigmoid. Medical care should be given until the age of 2 years, in expectation of surgical intervention later.

ALLEN, Santa Fe, N. Mex.

AN EXACERBATION OF HEPATITIS PRECIPITATED BY A NASAL OINTMENT AND ACCOMPANIED BY SWELLING OF MAMMARY GLANDS. FLORA PRIETO HUESCO, Acta pediat. españ. **12**:547 (June) 1954.

This is a very interesting report of a little girl of 8 years who had hepatitis. She recovered without any unusual delay, but because she had epistaxis of a rather alarming type she was given an ointment by a rhinologist. The hepatitis recurred, accompanied by swelling of the breasts, profuse leucorrhea, and genital hemorrhage simulating menstruation, which lasted four days. The ointment was found to contain diethylstilbesterol (Stilbestrol). After the use of the ointment was stopped, the symptoms disappeared. Urine assay revealed that she was excreting daily 20 R. U. hypophyseal gonadotropic hormones.

The author presents many questions regarding the mechanism of diethylstilbestrol on the liver. The nasal mucosa has long been known to stimulate gonads, but the exacerbation of the hepatitis may or may not have been related.

ALLEN, Santa Fe, N. Mex.

HEPATIC BIOPSY STUDIES. F. SALA PANISELLO, A. CASTELLANOS JR., and J. D. BLAIR, Arch. med. inf. **23**:317 (Oct.-Dec.) 1954.

The type of approach in liver puncture does not seem to be the decisive factor in determining fatal hemorrhagic complications. In this sense, incorrect manipulations for performing the puncture and changes of blood coagulation are more important.

When being carried out with a correct technique, liver puncture has proved to be a relatively harmless method, as is borne out by the statistics of most authors and by the case described.

The authors present their own experiences in 250 cases without a single fatal accident, carried out in children up to the age of 12 years; they stress the advantages of the intercostal approach, particularly in children and in the absence of manifest hepatomegaly.

FROM THE AUTHORS' SUMMARY.

OBSERVATIONS IN A CASE OF GLYCOGEN-STORAGE DISEASE OF THE LIVER. H. J. BEKIUS and T. H. J. HUISMAN, Maandschr. kindergeneesk. **22**:37 (Feb.) 1954.

A description is given of a case of glycogen-storage disease of the liver in a one year old boy. The child had had hypoglycemic convulsions very frequently. Treatment with corticotropin (ACTH), 12 mg. daily, increased the glucose content of the blood and the acetonuria disappeared. A diet rich in carbohydrates did not greatly reduce the convulsions, but when a diet rich in proteins was given, the glucose content of the blood remained above 70 mg. per 100 cc. and the liver reduced in size.

The effect of the oral and intravenous administration of glucose, fructose, and invert sugar upon their concentrations in the blood is described. Oral glucose and fructose administration caused an increase of their concentrations in the blood to high levels, which were maintained longer than normal.

Oral administration of glucose during treatment with corticotropin caused the same maximum level of glucose in the blood, despite the higher initial level, but the maximum concentration was maintained longer than without administration of corticotropin.

Oral administration of glucose and fructose caused an identical rise of the glucose content of the blood.

The synthesis of glucose into glycogen is probably reduced because of the high glycogen content of the liver.

VAN CREVELD, Amsterdam.

RECURRING PAROTITIS. E. D. A. M. SCHRETLEN and B. J. C. DEN HARTOG, Maandschr. kindergeneesk. **22**:397 (Dec.) 1954.

Relapsing parotid tumors are described. In children this disease makes its appearance as a relapsing parotitis, which has its ductogenic and—very rarely—glandular origin. Psychogenic and psychoallergic forms also exist.

The sialograms are of considerable importance with regard to the differentiation of the syndromes discussed. The microscopy of the parotid gland and duct is described.

FROM THE AUTHORS' SUMMARY.

CARE OF LYMPHOSARCOMA OF THE DUODENUM IN A BOY OF SIX YEARS. G. van OOTEGHEM, Maandschr. kindergeneesk. **22**:408 (Dec.) 1954.

A case is described of lymphosarcoma of the small intestine, occurring in a boy 6 years old, presenting the symptoms of chronic intussusception.

FROM THE AUTHOR'S SUMMARY.

REDUPLICATION CYSTS OF THE ESOPHAGOGASTROINTESTINAL TRACT. L. D. EERLAND, Nederl. tijdschr. geneesk. **98**:339 (Feb. 6) 1954.

The author describes two cases of cysts connected with the esophagogastrointestinal tract. In one case, a cyst had a patent connection with the duodenum, causing intermittent melena and attacks of abdominal pain with vomiting. In the second case, x-ray of thorax showed a round shadow in the left lower longfield. This was caused by a mediastinal cyst connected with the esophagus and passing through the diaphragm to the middle of the lesser curvature of the stomach. These cysts may occur anywhere along the digestive tract. Eighty cases are mentioned in literature. Surgical removal is indicated.

VAN CREVELD, Amsterdam.

AN EXPLOSIVE OUTBREAK OF INFECTIOUS HEPATITIS IN AN INSTITUTION. G. D. HEMMES, Nederl. tijdschr. geneesk. **98**:1001 (April 10) 1954.

In the period 1925 to 1940 some epidemics of infectious hepatitis have occurred in Holland, but most cases of infectious hepatitis were sporadic ones. Since 1944, the morbidity of infectious hepatitis has been higher and is now still rising. Fecal contact is the most important route of transmitting the infection.

An epidemic of infectious hepatitis occurred in a mental institution in the spring of 1953. The first case was observed March 29. The second case followed on April 8, and there was one case on April 15, 21, and 22, respectively. The time distribution of the other cases is as follows: April 26 to May 2, 7 cases; May 3 to 9, 24 cases; May 10 to 17, 14 cases; May 17 to 23, 6 cases; May 24 to 30, 8 cases, and 4 more cases in the first week of June. Most cases occurred among the 114 patients between the ages of 3 and 9 years. Among the five patients 10 to 22 years of age, one dubious case of hepatitis was noted, and 3 of the 65 members of the staff fell ill.

The first patient with hepatitis is thought to be the source of infection in this outbreak. One of her roommates helped in the kitchen, and it was her task to distribute the milk for the children. This may explain the short duration of this epidemic of hepatitis.

VAN CREVELD, Amsterdam.

JUVENILE LIVER CIRRHOSIS CAUSED BY ENDOPHLEBITIS OBLITERANS HEPATICA. G. BRAS, B. JELLIFFE, and K. R. STUART, Nederl. tijdschr. geneesk. **98**:2341 (Aug. 21) 1954.

The authors report on 12 Jamaican children with clinical symptoms of acute swelling of the abdomen, enlargement of the liver, ascites, and, in some instances, icterus. These children were suffering from relative malnutrition but did not belong to the poorest classes, among whom kwashiorkor and marasmus prevail.

Three children died. The others improved after a low-protein as well as after a high-protein diet. Histological examination of the liver (after biopsy or postmortem examination) showed obliteration of the branches from the hepatic vein, caused by swelling and afterward increasing fibrosis of the intima. Generally the central sinuses and sinusoids were enlarged. The parenchyma showed fatty degeneration, and sometimes cirrhosis occurred. Neoformation of liver cells was seen near the bigger hepatic veins. The syndrome resembles that of the infantile cirrhosis in India.

VAN CREVELD, Amsterdam.

A Case of Pancreatic Fibrosis in a Boy Eighteen Years Old. J. B. Lips and A. H. Wiebenga, Nederl. tijdschr. geneesk. **98**:2500 (Sept. 4) 1954.

The history is presented of a 18-year-old boy who at the age of 2 days was suspect for a meconium ileus and when 4 years old had diarrhea with a high fat content of the stools. On a low-fat and high-protein diet the feces were voluminous and clayish. From 6 years on he coughed slightly. When 16 years old there were deviations on the x-ray picture, and in 1953 he suffered from bronchopneumonia. During the last two years the boy received protamine zinc insulin injections for his diabetes mellitus. The duodenal juice contained no pancreatic ferments. The sputum was rich in a hemolytic Staphylococcus aureus. No prophylactic antibiotic therapy was applied.

van Creveld, Amsterdam.

Nervous Diseases

The Surgical Management of Subdural Effusions and Their Accompanying Neomembranes in Infancy. Jonathan M. Williams and Harold Stevens, Ann. Surg. **139**:287 (March) 1954.

The authors emphasize that factors other than trauma may be responsible for the subdural accumulation of fluid and neomembrane formation.

Bacterial meningitis, chronic debilitating diseases, infections elsewhere in the body, and infantile diarrheas, in some obscure way must interfere with the delicate homeostasis of intracranial isotonicity and trigger a sequence eventuating in subdural hemorrhage or exudate followed by membrane formation.

When a subdural effusion appears, the child becomes fretful and frequently shows evidences of developmental regression. Indolent low-grade fever may appear even though the spinal fluid has completely cleared. Listlessness and irritability are evident.

When subdural punctures reveal the presence of xanthochromic fluid with a high protein content, it is reasonable to infer that a neomembrane has formed and may be encapsulating and constricting the growing brain. Surgical treatment should then be considered.

The authors give in detail preoperative, surgical, and postoperative treatment.

Bantin, Omaha, Nebr.

Spasticity: Its Nature and Treatment. Milton G. Levine and Herman Kabat California Med. **80**:306 (April) 1954.

There are a number of physiological means of relaxing spasticity, including active resistive exercise, cold hydrotherapy, heat, electrical stimulation of antagonistic muscles, passive stretch in diagonal movement patterns, and the Bechterew's reflex. Although none of them will cure spasticity, temporary relaxation may permit a patient to achieve better functioning of an affected joint. The choice of procedure will depend on the nature of the lesion and the muscular distribution of the spasticity.

Pryor, Redwood City, Calif.

Pyridoxine Depencency: Report of a Case of Intractable Convulsions in Infant Controlled by Pyridoxine. Andrew Hunt Jr., Joseph Stokes Jr., Wallace W. McCrorry, and H. H. Stroud, Pediatrics **13**:140 (Feb.) 1954.

A case of convulsions in an infant requiring pyridoxine for their control has been described. On oral dosage of pyridoxine, 2 mg. per day, seizures have now been controlled for 21 months, with no increase in dosage being required. A continuing need for pyridoxine is demonstrated by the recent reappearance of seizures following a short lapse of pyridoxine administration.

In the absence of biochemical evidence of pyridoxine deficiency, as measured by xanthurenic acid excretion following a tryptophan load and with meager clinical evidence for the complete picture of such deficiency, the authors prefer to designate this phenomenon "pyridoxine dependency." The hypothesis has been propounded that this infant suffers a metabolic anomaly in pyridoxine metabolism resulting in convulsions in the absence of regular dietary pyridoxine supplements.

From the Authors' Summary.

BILIRUBIN ENCEPHALOPATHY. WILLIAM J. WATERS, DAN A. RICHERT, and HELEN H. RAWSON, Pediatrics **13**:319 (April) 1954.

Peripheral blood specimens from cases of varying degree of clinical severity of hemolytic disease of the newborn infant have been examined spectrophotometrically, and a curve consistent with the presence of bilirubin was found in each case.

Extracts of the pigmented brain areas from five cases of hemolytic disease of the newborn infant who died with clinical signs of brain damage were examined spectrophotometrically, and in each instance a curve consistent with bilirubin was obtained. An extract from comparable sections of brain not appearing grossly pigmented contained essentially no such pigment when examined spectrophotometrically.

Crystals were obtained from a chloroform extract of pigmented brain areas and when redissolved showed typical curve for bilirubin.

A positive van den Bergh test was obtained on the extract solution.

FROM THE AUTHORS' SUMMARY.

DIPHTHEROID MENINGITIS COMPLICATED BY HYDROCEPHALUS. M. C. JOSEPH, Proc. Roy. Soc. Med. **47**:131 (Feb.) 1954.

Meningitis occurring in an 11-day-old infant was due to a pure culture of diphtheroid. Treatment with chlortetracycline (Aureomycin) and streptomycin appeared to result in great improvement. Four weeks after discharge hydrocephalus suddenly appeared and was treated surgically. Improvement was noted but was not complete.

McGUIGAN, Evanston, Ill.

CHAIN-SYNERGIES IN NEUROMUSCULAR RE-EDUCATION. A. OBHOLZER, South African M. J. **28**:105 (Feb. 6) 1954.

The author discusses briefly kinetic therapy in the orthodox treatment of cerebral palsy. He considers the present method of attempting immediate isolated muscle contraction erroneous because it depends on good intelligence and fair attention span, which are rarely present in spastic children, and also because there is no neurophysiological basis for such isolated muscle contractions.

He feels that the use of chain synergies, or mass movement, is rational and offers a neurophysiological basis of resisted chain-synergy treatment.

McGUIGAN, Evanston, Ill.

MULTIPLE SCLEROSIS IN CHILDHOOD. M. BONDUELLE, P. BOUYGUES, and C. SALLOU, Presse méd. Supp. 27, p. 563, April 14, 1954.

Multiple sclerosis is infrequent, if not exceptional, in children, at least in its classic form with such a chronic development as seen in adults. A few cases are, however, to be found in the literature, and one more is here reported as unquestionably ascribable to this condition. It has been developing for 12 years in a boy now 19 years old, with concurrence of such typical signs as optic neuritis, cerebellar and pyramidal syndromes, dysesthesia, loss of certain reflexes, some apathy, and euphoria.

The authors discussed in the diagnosis differentiation from "pseudosclerose en plaque" possibly due to hereditary syphilis, cerebellar heredoataxia, leucoencephalitis.

"Acute disseminated encephalitis" raises a problem concerning its possible identity with multiple sclerosis, although its symptomatology is quite different. But the problem in fact covers the whole nosologic concept of leucoencephalitis and the limitation of multiple sclerosis, which cannot be resolved by the histologic criteria.

It is necessary to confine the problem to the study of the chronic forms in children. These forms may be considered very rare in them but with no possibility of determining an accurate percentage. They compare with the form encountered in young adults in respect with the mode of onset, the symptomatology, the course, and the general prognosis. But this form of multiple sclerosis is not the only one to be seen in children.

FROM THE AUTHORS' SUMMARY.

A FAMILIAL DYSTROPHY. J. HOZAY, Rev. neurol. **89**:245, 1953.

The report concerns two siblings who were offspring of a consanguineous marriage. The characteristics of this maldevelopment were that although the patients were normal at birth, at 3 years of age an arrest of growth of all four extremities occurred. The large toes were

relatively small in proportion to the rest of the foot. Later, there developed a reduction in the size of the distal two-thirds of the extremities. The bony structures were disproportionately smaller than the soft tissues, with consequent folding over of the skin. Trophic disturbances of the skin appeared in the form of ulcerations and keratoses. There was no alteration in sensation, such as one might expect in syringomyelia. The facial maldevelopment consisted of a larger-than-normal biparietal and bizygomatic diameter, micrognathia, and infantile dental development. One of the siblings was mentally defective, but the other was normal. There were numerous freckles over the face and extremities.

BERLIN, Mount Vernon, N. Y. [A. M. A. ARCH. NEUROL & PSYCHIAT.].

CASE OF INFANTILE FOCAL EPILEPSY TREATED BY FRONTAL LOBECTOMY. BRAVO, LEY, and C. SÁINZ DE LOS TERREROS, Acta pediát. españ. **11**:855 (Sept.) 1953.

The case presented is that of a 2½-year-old girl with a focal epilepsy which was not amenable to any of the anticonvulsant drugs. The EEG showed a focus in the right frontal area.

Details of attacks, means of diagnosis, and the type of surgical intervention used are all described. Removal of a portion of the frontal lobe on the right side resulted in complete recovery. The pathologist's report showed the presence of astrocytes and a glioma, with some areas of degeneration in both the grey and the white nerve tissue of the frontal cerebral lobe.

There has been no deleterious effect in the physical and mental development of the child.

ALLEN, Santa Fe, N. Mex.

NORMAL CEREBROSPINAL FLUID IN EARLY INFANCY. JOSÉ RÁUL VÁSQUEZ, ERNESTO TOMÁS SOJO, and JUAN DUILIO VIDAL, Rev. Soc. puericult. Buenos Aires **19**:161 (Oct.-Dec.) 1953.

We have determined the physical characteristics and the chemical and cytological composition of spinal fluid in 100 children, between 1 and 24 months of age, who fulfilled the necessary requisites, according to our criterion, for normal spinal fluid.

The liquid was obtained after the child had a fasting diet, and the examination was made immediately, to eliminate all possible causes for error (glycolysis, cytolysis, etc.).

The statistical mathematical system was applied to obtain the results. In each group of determinations, the ciphers obtained are compared with those published by other authors, and the difference with our results is shown.

A comparative study has been done to establish whether in the first five months of life, differences are to be found according to the diet to which the child has been submitted.

Tables and lists have been made, with the data shown by age in months. For each factor considered, the curves of the arithmetic average have been studied, as well as the maximum and minimum ciphers and the normal zone, determined by the values of the standard deviation.

FROM THE AUTHORS' SUMMARY.

NON-BACTERIAL MENINGO-ENCEPHALITIDES IN CHILDREN. IVAR NILSBY, Acta pædiat. Supp. 95, Jan., 1954.

Clinical experience suggests that meningoencephalitis in childhood is more common than formerly supposed, and it has been suggested that as the symptoms are often mild and non-characteristic, at least in children, many cases still remain concealed unless the possibility of mild meningoencephalitis be continuously borne in mind.

It has also been stressed that even these mild forms of meningoencephalitis are often followed by sequels, especially behavior disorders, but hitherto no investigations, at least not on a large series, have been available to support this belief.

With this in mind, all of the cases of meningoencephalitis seen at the Pediatric Clinic, University Hospital, Lund, and classed as apparently spontaneous meningoencephalitis, meningoencephalitis after respiratory tract infections, and central nervous system involvement associated with varicella were selected. These cases were studied in order to form a more detailed opinion of the clinical picture of these meningoencephalitides (and as far as varicella is concerned, of the frequency of central nervous system involvement). The investigation included a review, at which the children were examined neurologically, psychically, psychometrically, and regarding their social adjustment. The observations made were compared with the control series. Unlike earlier series on record, the present material included a large percentage of apparently mild cases of meningoencephalitis and, above all, the results were judged in relation to a control series.

Central nervous system involvement in association with apparently mild infections of the respiratory tract was found to be fairly common, especially in children below one year of age.

The clinical picture of spontaneous meningoencephalitis was not found to differ from that of postcatarrhal meningoencephalitis; these groups did, however, differ with respect to age distribution and seasonal occurrence. This suggests the possibility of difference in etiology, i. e., a viral origin for the spontaneous group and a toxic origin for the postcatarrhal group.

The early prognosis was as a rule good.

Of the 102 cases, 3 occurred during the time of the investigation. In all three, the clinical picture was exactly the same as that described for the first attack. This suggests decreased local resistance following the first injury, a decrease that becomes apparent if the brain is exposed to some injurious factor—inflammatory or toxic.

Comparison of the patients of the spontaneous and postcatarrhal groups at the review showed no difference regarding neurologic, psychiatric, or psychometric symptoms or social adjustment. These two groups were therefore taken together in the comparison with the controls. This comparison revealed a statistically significant difference between the patients and the controls regarding neurologic and emotional symptoms, mental development, and most of the special tests used at the psychometric investigation. A statistical difference was also demonstrated regarding social adjustment. Many of the patients had difficulties at school despite a normal intelligence quotient. These school difficulties were due to a certain extent to emotional disturbances, mostly to special impairments, inability to integrate different perceptions, impaired memory, and impaired attention. As the patients and the controls were comparable, with the exception that the patient had had known meningoencephalitis, the difference between the observations made at the review must be regarded as sequels after meningoencephalitis.

The frequency of brain injury in the patients, as compared with that in the controls, was taken as a measure of the frequency of sequels from meningoencephalitides. As judged in this way, the frequency of sequels after these meningoencephalitides was about 35%.

All of the sequels showed a strong tendency to subside and to become less pronounced with increasing age. Those symptoms that persisted were as a rule mild and meant only a slight handicap for the patient, and only in a few isolated cases were the symptoms so severe as to lead to disability or social maladjustment.

The sexes were not found to differ regarding prognosis. Neither did the age at the time of the onset appear to be of prognostic importance. In the event of symptoms of meningitis only, or of meningoencephalitides of rapid and mild course, the prognosis appears to be more favorable. Central nervous system involvement was found to be fairly common in varicella (22%). It was observed as a mild clinical form of meningoencephalitis or as asymptomatic pleocytosis. At review none of these children showed definite sequels attributable with certainty to the primary disease. In one child, however, severe, though transient, behavior disorders were noted.

The cell and protein content of the cerebrospinal fluid and the effect of previous puncture were studied on normal children.

On the basis of these studies, the upper normal limit for the cell count for children above 3 months of age may be taken as three cells per cubic millimeter.

For children below 3 months of age the upper limits for both the cell count and the protein content may be somewhat higher.

Earlier lumbar puncture has no effect on the protein content, but if the interval between two consecutive punctures is less than eight days, the cell count may be increased.

FROM THE AUTHOR'S SUMMARY.

PNEUMOENCEPHALOGRAPHY IN A PEDIATRIC DEPARTMENT, WITH SPECIAL REFERENCE TO BRAIN ATROPHY. J. VESTERDAL, K. E. FOGHT-NIELSEN, and G. THOMSEN, Acta pædiat. **43**:120 (March) 1954.

The author reviews 214 consecutive encephalograms from children mostly suffering from epilepsy, oligophrenia, cerebral palsy, or various combinations of these symptoms. Sixty-two patients had normal encephalograms, while almost all the others had more or less pronounced brain atrophy. Except in the cases with one-sided symptoms, no conspicuous correlation existed between the nature of the symptoms or the electroencephalograms and the character of the brain atrophy, except that most epileptics had normal pictures. Very often there was a disproportion between the severity of the clinical symptoms and the degree of brain atrophy visible on the encephalogram. In 60% of the patients with hemiplegia or Jacksonian seizures, asymmetrical atrophy of the brain was found. Agenesis of the corpus callosum was found in two cases. That

no disease which could be treated neurosurgically was found in this series to be, at least partially, accounted for by our practice of immediate transfer to the neurosurgical department of all cases of brain tumour.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

EFFECT OF THYROIDECTOMY ON HYPERTENSION, NEPHROSCLEROSIS AND CARDIAC LESIONS PRODUCED BY DESOXYCORTICOSTERONE ACETATE (DCA) TREATMENT IN THE RAT. E. SALGADO, Endocrinology **55**:377 (Oct.) 1954.

It appears that thyroidectomy can inhibit the development of hypertension, nephrosclerosis and cardiac nodules induced by desoxycorticosterone acetate (DCA) overdosage. On the contrary, periarteritis nodosa is actually aggravated in the absence of the thyroid gland. This means that in the rat periarteritis nodosa is not a consequence of hypertension only.

JACOBSEN, Buffalo.

STUDIES OF ACTH ACTION UPON PERFUSED BOVINE ADRENALS: CORTICOSTEROID BIOSYNTHESIS IN ISOLATED GLANDS MAXIMALLY STIMULATED WITH ACTH. I. A. MACCHI and O. HECHTER, Endocrinology **55**:387 (Oct.) 1954.

The primary object of the authors was to obtain an in vitro adrenal system wherein certain aspects of corticotropin (ACTH) action upon corticosteroid biosynthesis might be studied in direct fashion. The results presented in this paper demonstrate that the isolated perfused adrenal of the cow is a satisfactory system for demonstrating the corticosteroidogenic activity of corticotropin. The cow adrenal perfused with homologous citrated blood responds to added corticotropin by a tenfold to nineteenfold increase in corticosteroid production.

JACOBSEN, Buffalo.

THE NECESSITY FOR PROGESTERONE WITH ESTROGEN FOR THE INDUCTION OF RECURRENT ESTRUS IN THE OVARIECTOMIZED EWE. T. J. ROBINSON, Endocrinology **55**:403 (Oct.) 1954.

The results of these experiments suggest that the role of progesterone is more fundamental than merely estrogen sparing.

It is concluded that alternate progesterone-estrogen influence is necessary for regular cyclic estrous behavior in the ewe.

JACOBSEN, Buffalo.

EFFECT OF CHRONIC PITRESSIN ADMINISTRATION ON ELECTROLYTE EXCRETION IN NORMAL DOGS AND IN DOGS WITH EXPERIMENTAL ASCITES. JAMES O. DAVIS, DAVID S. HOWELL, and ROBERT E. HYATT, Endocrinology **55**:409 (Oct.) 1954.

The present studies were undertaken to determine the effect of chronic vasopressin injection (Pitressin) administration on electrolyte excretion in normal dogs and in dogs with ascites produced by constriction of the thoracic inferior vena cava. The relation of the changes in electrolyte excretion to adrenocortical function in animals with ascites has been evaluated by injection of vasopressin injection in adrenalectomized dogs with thoracic inferior caval constriction.

It is indicated that vasopressin injection had no direct effect on renal tubular transport of electrolytes.

JACOBSEN, Buffalo.

JUVENILE THYROTOXICOSIS: RESULTS OF TREATMENT IN 30 CASES. RICHARD F. ALLEN, EDWARD ROSE, and ELIZABETH KIRK ROSE, Pediatrics **14**:38 (July) 1954.

Results of treatment are presented in 30 thyrotoxic children whose symptoms appeared prior to the age of 15 years.

Fifteen patients received thyroid irradiation, with or without stable iodine, and 15 received prolonged treatment with antithyroid compounds, with or without stable iodine.

Among the 24 patients in whom the final results of treatment could be fairly assessed, satisfactory remissions were obtained in 17 (70.8%). Approximately similar results were obtained in children who were irradiated and in those who received antithyroid compounds.

Satisfactory remissions were obtained in five of the six patients subjected to thyroidectomy.

Two cases of unusual interest are described. Reasons for the present conservative policy in the treatment of juvenile thyrotoxicosis are stated.

FROM THE AUTHORS' SUMMARY.

GENITAL FINDINGS IN PSEUDOHERMAPHRODITISMUS FEMININUS OF THE CONGENITAL ADRENOGENITAL SYSTEM. A. PRADER, Helvet. pædiat. acta **9**:231 (July) 1954.

A study of the genital malformation in girls with the congenital adrenogenital syndrome, based on 19 personal and many additional observations from the literature, reveals five different genital types. Common to all types is the hypertrophy of the clitoris. In Type I the vulva is normal. In Type II the vestibulum is deep and funnel-like. In Type III to IV there is a single perineal urogenital orifice, varying in size. In Type V the urogenital orifice is at the tip of the clitoris. The labia minora are absent in Types III to V., and the scrotum-like labia majora are increasingly fused. The vagina opens directly to the outside in Types I to II and into the urethra-like urogenital sinus in Types III to V. The internal genitalia are female with the exception of a prostate in Types III to V.

Types II to IV occur frequently, Types I and V, rarely. The abnormal genital development starts probably between the fetal age of 10 (Type V) and 16 weeks (Type II) or later (Type I).

From the study of siblings it seems that the whole syndrome, as well as the three variable separate symptoms: (1) genital type, (2) salt-losing syndrome, and (3) hypertension, is genetically determined. The salt-losing syndrome is much more rarely associated with Types I to III than with Types IV to V. On the other hand, no close relationship exists between the degree of genital malformation and the degree of the other androgenic symptoms.

FROM THE AUTHOR'S SUMMARY.

STUDY OF HYPOTHYROIDISM IN CHILDHOOD USING RADIOACTIVE IODINE. JAMES H. HUTCHISON, Maandschr. kindergeneesk. **22**:299 (Sept.) 1954.

The use of radioactive iodine tests has increased our understanding of some forms of hypothyroidism occurring during childhood.

The results of such tests in two groups of hypothyroid children have been outlined.

In the first group, of 13 goitrous children, it has been suggested that there was an intrinsic, and in some instances a familial, defect in the synthesis of the thyroid hormone.

In the second group, of two patients, the hypothyroidism was shown to be due to the presence of an ectopic thyroid gland which, as the child developed, proved unable to meet the body's needs for hormone.

FROM THE AUTHOR'S SUMMARY.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

TWELVE CASES OF LYMPHOBLASTOMA IN CHILDREN. GEORGE M. MAXWELL, Arch. Dis. Childhood **29**:155 (April) 1954.

Twelve cases of lymphoblastoma in children are presented; none was thought to be of the Hodgkin variety. The symptoms and physical signs are seen to be protean and in some cases bear no relation to widespread anatomical lesions. The process in the majority is rapidly fatal. The difficulties of diagnosis are discussed, the initial picture being misleading, here varying from actinomycosis of the jaw, tuberculous peritonitis, and benign lesion of the caruncle to scrofula.

KELLY, Milwaukee.

ETIOLOGY OF STILL'S DISEASE. E. MAYERHOFER, Ann. pædiat. **183**:203 (Oct.) 1954.

An attempt is made to simplify the etiology of Still's disease. The causes of 22 cases observed by the author and of others found in the literature can be grouped as follows: (1) infections; (2) allergy; (3) noninfectious polyvalent causes; (4) a deficient RES; (5) a stress adaptation syndrome (Selye).

FROM THE AUTHOR'S SUMMARY.

HOW CAN WE PREVENT THE DEVELOPMENT OF THE SO-CALLED CONGENITAL LUXATION OF THE HIP JOINT. JULIUS HASS, Wien. klin. Wchnschr. **66**:621 (Sept.) 1954.

The luxation itself of the hip joint is not congenital. A "dysplasia" as described by Hilgenreiner is congenital and can be recognized earlier. The dysplasia manifests itself in the region of the acetabulum and in the coxal end of the head of the femur, but most important for the early diagnosis is the acetabular index. An abduction splint is described. Twenty-four cases were treated by the author, starting at the age of 1½ to 8 months with a period of observation exceeding five years. In all an anatomical and functional restoration was recorded.

AMBERG, Rochester, Minn.

CHILDREN WITH LUXATION OF THE FEET. MARIO OLIVERA DEVISO, Rev. españ. pediat. **10**:65 (Jan.-Feb.) 1954.

The author discusses the difference between the physiological flat feet and the child with serious deformity who should always be seen by an orthopedist.

ALLEN, Santa Fe, N. Mex.

GENERALIZED MYOSITIS OSSIFICANS PROGRESSIVA. M. A. MORILLO ATENCIO, Arch. med. inf. **23**:238 (July, Aug., Sept.) 1954.

The author presents a case of generalized progressive ossifying myositis, followed up during the years. The disease was discovered by the patient's mother whose attention was called to a small but painful swelling in the back. The tumor was also noticed by other women of the neighborhood, and as the swelling hardened, it led at last to obstruction of the respiratory movements. What was unusual was the normal development of the patient, the laboratory findings, and the absence of glandular alteration.

All therapeutic measures, including radiotherapy, proved unsuccessful. The radiological fiindings were conclusive, proving the presence of a generalized progressive ossifying myositis.

The x-ray diagnosis was confirmed by the anatomopathological findings.

FROM THE AUTHOR'S SUMMARY.

Psychology and Psychiatry

THE PHYSICIAN, THE PARENT AND THE RETARDED CHILD. CHARLES LUDWIG and MARSHALL PORTER, California Med. **88**:394 (May) 1954.

The problem of the retarded child and his parents is one confronting practicing physicians more and more frequently. Current estimates indicate that state hospital facilities for retarded persons in California are short nearly 6000 beds. There are long waiting lists for available facilities. Many families are in desperate need of help. To advise a family to send their child to a state hospital is not a real solution or one possible in the great majority of instances. The responsibility of the physician goes beyond this. Parents' groups have developed in the last few years and are making a real contribution to a resolution of the problem. Local community resources have increased and will further increase. A more accurate clinical understanding of the retarded child has been formed, and his treatment needs to be defined more clearly. Physicians, parents, and community and state agencies must work together to effect a coordinated program.

PRYOR, Redwood City, Calif.

A PERSONALITY INVENTORY ITEM ANALYSIS OF INDIVIDUALS WHO STUTTER AND INDIVIDUALS WHO HAVE OTHER HANDICAPS. FRANCIS WALNUT, J. Speech & Hearing Disorders **19**:220 (June) 1954.

The short form of the Minnesota Multiphasic Personality Inventory was administered to 141 high school students or to students of high school age divided into four groups: a control group, a group of stutterers, a group of crippled persons, and a group with cleft palate. All were within the theoretical normal range of personality. The stutterers had increased indications of paranoia and depressive tendencies but did not differ significantly from the crippled and the cleft-palate groups in personality. The study did not indicate whether stuttering precipitated abnormal personality or vice versa.

PALMER, Wichita, Kan.

MENTAL RETARDATION. WILLIAM L. MUSSER, South. M. J. **47**:77 (Jan.) 1954.

This is a worthwhile review article which should be read by all pediatricians and general practitioners. The author emphasizes that at least half of the cases of mental retardation are due to causes which are possibly preventable or whose incidence could continually be reduced. He points out how important it is for physicians to pass on to the parents of retarded children a sane and rational understanding of the problem of retardation. He urges that consideration always be given to home care before recommending institutional care. Mention is made of the formation of the National Association for Retarded Children.

LOGAN, Rochester, Minn.

MONGOLISM: PROGNOSIS OF PREGNANCIES AFTER THE BIRTH OF A MONGOLOID; OBSERVATIONS WITH REGARD TO THE ETIOLOGY. O. THALHAMMER, Wien. klin. Wchnschr. **66**:165 (March 12) 1954.

Mongoloid children were seen in 196 families. In later pregnancies 95% of infants born at term did not have this disorder. In about 10% of later pregnancies abortion may occur. Even so, non-Mongoloid infants can be the result of later pregnancies. Exogenous fetal injuries during the first three months of pregnancy may perhaps be concerned in the etiology of Mongolism.

AMBERG, Rochester, Minn.

THE INFLUENCE OF PHENYLALANINE INTAKE ON THE CHEMISTRY AND BEHAVIOUR OF A PHENYLKETONURIC CHILD. HORST BICKEL, JOHN GERRARD, and EVELYN M. HICKMANS, Acta pædiat. **43**:64 (Jan.) 1954.

Phenylketonuria is not an uncommon cause of mental deficiency (there are probably 1600 cases in Great Britain alone). On the supposition that the high level of phenylalanine or its breakdown products in the blood and cerebrospinal fluid might be responsible for the mental retardation in this disorder, we have treated a 2-year-old child with a diet low in phenylalanine. The introduction of this diet was associated with an appreciable improvement in the patient's mental status and a fall in the level of phenylalanine in the blood and urine. When phenylalanine was again given in fairly large amounts, there was an immediate and dramatic deterioration in the child's mental and biochemical condition. A similar phenylalanine intake produced no clinical reaction in a control child.

The main source of amino acids in the diet was an acid casein hydrolysate which was specially treated to remove phenylalanine. The aim of the phenylalanine-poor diet was to keep the phenylalanine blood level as near the normal range as possible. The preparation of such a diet presents little difficulty if a phenylalanine-free casein hydrolysate is available. Its value in the treatment of other children is at present being investigated; it seems reasonable to assume that patients in the first two years of life will benefit most.

FROM THE AUTHORS' SUMMARY.

Diseases of Genitourinary Tract

TREATMENT OF URINARY TRACT INFECTION. DEAN PARKER, J. A. M. A. **154**:972 (March 20) 1954.

A urinary infection in a young child should be properly diagnosed, with use of sound surgical principles, and the elimination of foci of infection should be considered.

KIMBALL, Evanston, Ill.

CONSIDERATIONS IN BILATERAL CRYPTORCHISM. C. A. HOOKS, J. Louisiana M. Soc. **106**:51 (Feb.) 1954.

Careful evaluation of the cryptorchid person is necessary to preserve testicular functions. Preservation of spermatogenesis is important. In every case of real or apparent failure of the testes to descend, the physicians must determine whether simple testicular retention or sexual dimorphism is present. Wrong decisions may result in infertility in the first instance and interference in the second instance with optimum sociologic adjustment.

MCGUIGAN, Evanston, Ill.

URETEROCELE IN A GIRL OF NINE YEARS. M. BETTEX, Helvetica paediat. acta **9**:20 (April) 1954.

Retention of urine and chronic pyelitis caused by ureterocele, i. e., enlargement of the intravesical part of the ureter above a congenital stenosis of the ostium, should be taken more into consideration. The symptoms are typical. The diagnosis is secured by cystography and cystoscopy. Without treatment, frequently double-sided hydronephrosis develops and the prognosis is unfavorable. With early surgical treatment—endoscopial and transvesical incision of the uretercole—restitutio ad integrum or at least clinical recovery with stationary hydronephritis can be obtained. This intervention prevents the need for nephrectomy in most cases.

FROM THE AUTHOR'S SUMMARY.

Books

Epilepsy and the Functional Anatomy of the Human Brain. By Wilder Penfield and Herbert Jasper. Price, $16. Pp. 896. Little, Brown & Company, 34 Beacon St., Boston 6, 1953.

This volume is a very important contribution to the better understanding of a perplexing problem. Much of the material in the volume is based on the authors' personal observations at the Montreal Neurological Institute, where their work on seizures and localization is well known. The information is fundamental and gives perhaps the most comprehensive discussion on the subject to date. The chapters include a historical introduction, definitions and classifications, cortical localization, subcortical interrelationships, electrophysiology and experimental epilepsy, clinical observations on epileptic mechanisms, epileptogenic lesions, somatic motor seizures, and sensory, autonomic, psychical, and centrencephalic seizures. Much of the material is basic neurophysiology, but the orientation is definitely clinical. Of particular interest to the pediatrician is the excellent chapter on diagnosis and medical treatment, by Dr. Francis McNaughton. The chapters on electroencephalography (Jasper) and cranial roentgenography (Penfield) are most informative and remarkably comprehensive. The chapters on electrocortigraphy (Jasper) and surgical therapy (Penfield) present an excellent summary of these subjects. The social and emotional aspects of the problem of epilepsy are barely discussed but perhaps are summed up in the concluding paragraph of the book, by Penfield: "Throughout the analysis of every case, the clinician should be first and foremost, a wise physician and an understanding friend to the patient. He should weigh for him the chances for success by surgery and balance this against the best that conservative treatment can promise. He must see the whole problem in the perspective of the patient's own outlook on life." This volume can be heartily recommended as a most significant addition to the medical literature, particularly to all persons concerned with the problem of seizures.

Die Pathogenese des Icterus gravis neonatorum. By Helmut Patzer. Price, 5.40 Deutsche marks. Pp. 98, with 5 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O (American Zone); Agent for U. S. A.: Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

Of the 98 pages of the monograph on icterus gravis neonatorum, 14 are devoted to a historical review. It is stated that since the discovery of the Rh factor, no attention has been given anywhere to the question of whether a pathogenetic relationship exists between Rh-conditioned and other forms of icterus neonatorum which clinically may be very similar or identical. The author utilizes 17 cases of familial icterus gravis neonatorum, of which he was able to observe 7 personally. Various clinical and pathological aspects are discussed including consideration of the capillary fragility, coagulation and bleeding factors, and the multiplication of hematopoietic areas in liver and spleen and the appearance of such areas in other localities. The theme of the presentation is that the main feature in the pathogenesis is to be seen in the disorder of the permeability of the capillaries (permeability pathology of Eppinger). This increased permeability is due to the antigen-antibody reaction and hemolysis. Such a disorder of the permeability may not always be recognizable morphologically. A difference in the sensitivity of various capillary beds may explain the variable participation of various organs. Furthermore, the capillaries of the fetus and young infant react more readily to injuries and in a different manner than later in life. The cellular lesions of liver and other organs are all secondary to the disordered capillary permeability. The same holds true for forms of severe icterus of the newborn which are not Rh conditioned, such as the septic forms, the infectious form (Kleinschmidt), icterus prolongatus (Yllpö and Lange), icterus of connatal syphilis, and icterus of the premature infant. It is concluded that icterus gravis neonatorum is not exclusively specific to Rh incompatibility but is a reaction of the fetal organism or that of the young infant to a disorder of capillary permeability largely independent of the kind of stimulus which produces this disorder of permeability. The monograph is certainly not without interesting features.

Song of Life with Variations. By H. Ameroy Hartwell. Price, $5.00. Pp. 371. Bruce Humphries, Inc., 30 Winchester St., Boston 16, 1954.

This peculiar book is written for the general public. It will interest medical men only as a distraction.

The author says variety is the spice of life, and he presents a very varied menu. It would require the talent of an Escoffier to spice it acceptably. Apparently realizing this, he says that if it seems a bit incongruous, the reader may turn the pages until he is impressed. Like Robert Louis Stevenson, he seems to say,

"Go, little book, and wish to all,
Flowers in the garden, meat in the hall,
A bin of wine, a spirit of wit . . ."

The book may be divided into two parts or subjects: (1) "What's Wrong With Me?," and (2) "A Book of Poetry or Songs." A few tidbits or spiced morsels are interspersed.

In "What's Wrong With Me," he runs the gamut of orthodox symptoms and causes of diseases from abortion to wry neck. Though he advises not to diagnose or to treat yourself, the average reader is likely to pick from the list of symptoms something that will make him diagnose or keep him continuously on the road to the doctor.

Part 2 is a book of poetry, large enough to feed the multitude and to leave basketfuls of fragments.

There is no incompatibility between music and medicine. Before "The Song of Songs," music had charms. It has often been spoken of as an aid to sanity and equipment for living. The poet, Robert Graves, says that a well-chosen anthology is a complete dispensary of medicine for the more common mental diseases. Dr. Hartwell gives no advice to use medicines. Instead he says, "Read my poetry and see your doctor."

Poetry, like food, may be difficult to relish. It is a matter which must be left to the reader. We must accept the oft-quoted phrase, "*De gustibus non est disputandum.*"

The reader may forget the song, but he will not forget the singer.

The Meaning of Social Medicine. By Iago Galdston. Price, $2.75. Pp. 137. Harvard University Press, Cambridge 38, Mass., 1954.

The author presents much to make the reader think. It is worth while, even of you disagree with him.

Under the titles (1) What Is Social Medicine?, (2) The Failure of Modern Medicine, (3) Etiological Medicine, (4) Epidemic Constitution, (5) Mortality and Morbidity, and (6) Social Medicine and Medical Education, he discusses problems that have interested medical men and educators since the time of Hippocrates.

It is difficult to define social medicine or to tell what it embraces. It is not what people know as socialized medicine.

Some say it is a union of remedial and preventive medicine. However, remedial medicine and medical education is a Gestalt into which social medicine cannot be fitted. Social medicine is a larger Gestalt and is not fusible with remedial medicine. It can and should absorb curative medicine, which is not complete and has on the whole failed. Curative medicine gives too much weight to etiology and too little to the constitution and ecology of the patient. The doctor should know more of "eubiotic" medicine, more how to help the person achieve the best he is capable of in his experience in living. Curative medicine too often merely changes mortality to morbidity.

The physician should know much more than present-day medical education can possibly teach him. He should be not only a healer, but also a counselor. This function must be preeminent in social medicine.

Vaccines, sera, antibiotics, etc. may be good, but they cannot in and by themselves maintain health and well-being. Curative medicine, by deferring death, has indirectly and unwittingly produced a mounting burden of chronic illness. The public will in time demand something more effective and fundamental than curative medicine. They want a service that goes far beyond a prescription.

The author would have people live healthy and self-supporting up to the end, and then go

"All at once and nothing first,
Just as a bubble, when it bursts."

Pediatrics, he points out, is a specialty conceived in the spirit of social medicine. Psychiatry offers the best operating example of it.

The author is aware of the objections that may be raised and have been raised against his thesis.

Congenital Heart Disease: An Illustrated Diagnostic Approach. By Henry S. Kaplan, M.D., and Saul J. Robinson, M.D. Price, $12.50. Pp. 126, with 147 illustrations. McGraw-Hill Book Company, Inc., 300 W. 42d St., New York 36, 1954.

The authors state that this handbook is intended for the medical student and the general practitioner.

The first portion of the book consists of a discussion of the principles of differential diagnosis, including history, physical examination, simple laboratory procedures, roentgenographic study, electrocardiogram, angiocardiography, and cardiac catheterization.

The second portion of the book is a profusely illustrated atlas, in which the above principles of diagnosis are applied to the commoner congenital malformations of the heart. The material is well organized; the illustrations are well done; the printing is clear. A valuable feature is a drawing of the heart and great vessels superimposed on the x-ray films.

The medical student and the general practitioner, even though interested in congenital heart disease, can scarcely find time to read the numerous contributions which have been written largely for specialists.

This little volume does an admirable job of presenting the diagnostic approach to the more common congenital malformations of the heart. It will be a boon to the physician who wishes a brief introduction to the subject.

Diseases of the Retina. Edition 2. By Herman Elwyn, M.D. Price, $12.00. Pp. 713, with 243 illustrations (20 in color). Blakiston Company, 575 Madison Ave., New York 22, 1953.

This volume fills the need of both practitioners and students for a complete and systematic presentation of retinal diseases. The second edition retains the organization of the first, with the addition of three new chapters and complete revision of three others. There are 73 more illustrations and 126 more pages of material.

The book is divided into eight parts: (1) Retinal Diseases Resulting from Circulation Disturbances; (2) Retinal Diseases Resulting from Vascular Malformations; (3) Hereditary Degenerative Retinal Diseases; (4) Inflammatory Retinal Diseases; (5) Humors of the Retina; (6) Retinal Diseases Leading to Detachment; (7) Developmental Anomalies of the Retina; and (8) Radiation Injuries of the Retina. The author's concepts of vascular disease are revised to provide a comprehensive and up-to-date discussion of this important subject. A new chapter on retrolental fibroplasia has been added to the second part. The new introductory chapter to retinal heredodegenerations is excellent. The ocular tuberculosis chapter is revised to include recent work on pathogenesis. A short new chapter on ocular sarcoidosis is presented.

The author uses numerous summaries of cases from the literature to clarify his discussions and gives a profuse bibliography at the end of each chapter, with a good index at the end of the book. The pediatrician, as well as the internist, neurologist, and ophthalmologist, will enjoy and profit from reading this book as well as having it for reference.

Index of Differential Diagnosis. Edited by Arthur H. Douthwaite, M.D., F.R.C.P. Price, not given. Pp. 1046, with 731 illustrations, 200 of which are in color. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

The seventh edition of "Index of Differential Diagnosis" is a volume containing a tremendous amount of material with many beautiful illustrations. All fields of medicine are covered, and symptoms and signs are discussed in alphabetical order. In certain instances, the method of performing simple laboratory procedures is described.

Despite the efforts of the new editor and contributors to produce a worthwhile volume, this reviewer is disappointed in the book.

Terminology is not up to date. In the section on anemias, there is a long discussion on the value of the color index, but no mention is made of the importance of mean corpuscular volume,

mean corpuscular hemoglobin, or mean corpuscular hemoglobin concentration. The Coombs test is not listed in the description of hemolytic anemias.

In discussing ascites, chronic peritonitis, excluding tuberculous peritonitis, is stressed as an important entity. The statement is made that in patients with cirrhosis of the liver, if repeated abdominal tappings are necessary "the diagnosis should be replaced by that of perihepatitis." In the differential diagnosis of jaundice, "catarrh of the mucous membrane" of the common duct and pancreas is discussed. Another cause of jaundice is listed as emotional.

In the section on heart disease, rheumatic fever does not appear as a cause of aortic valve lesions. Among the causes of heart failure are listed "the primary alcoholic heart" and the "fibroid heart." In discussing adhesive pericarditis, every attempt is made to clarify the clinical picture, with no mention of venous pressure determinations.

In the differential diagnosis of backache, it is stated that protruded intervertebral discs are the cause of backache in 2% of cases.

Examples such as these emphasize the outdated terminology found throughout the text. It is the obligation of the new editor to be more critical of his material, not only from the standpoint of nomenclature, but also from the basic approach to clinical medicine.

The Allergic Child. By Harry Swartz M.D. Price, $3.95. Pp. 297. Coward-McCann, Inc., 210 Madison Ave., New York 16, 1954.

Dr. Swartz has written a scholarly and instructive book on the allergic child; it shows evidence of knowledge and experience. Here is found a great deal of information about all aspects of allergy: what it is, how it begins, the inhalant and food allergens, the influence of emotions on allergy, and the influence of allergy on the emotions. The chapter on the prevention of allergy is a stimulating one.

This reviewer, however, found it heavy going. It would be difficult reading for a mother unless she had exceptional ability or training in understanding a complicated subject.

It seems doubtful whether it is necessary or even wise for a mother to be informed about so many possibilities of disaster to the allergic child. The text is unduly frightening in its implications. A mother reading it may get the impression that in hay fever, sneezing frequently causes abdominal hernia with strangulation, or that in asthmatic children, bronchiectasis requiring pneumonectomy is common.

The list of diseases attributable at times to allergy is interesting and instructive to a physician, but it does not seem necessary to tell the mother that allergy may cause celiac disease, purpura, benign paroxysmal peritonitis, cataract, optic neuritis, meningitis, or intermittent hydrarthrosis.

It would seem to this reviewer that the knowledge of the author is not expressed in such a way as to be outstandingly useful in a book for the parents of an allergic child.

Directory of Pediatric Societies *

INTERNATIONAL

Eighth International Congress of Paediatrics

President: P. Plum Professor, M.D., Domus Medica, Kristianiagade, Copenhagen.

IV° Congreso Pan-Americano de Pediatria

President: Dr. Leonel Gonzaga.
General Secretary: Dr. Adamastor Barbosa.
Secretariat: Rua Dias da Rocha 25, ap. 602, Copacabana, Rio de Janeiro.
Place: Rio de Janeiro. Meeting held Aug. 1-7, 1954.

IV° Congreso Sudamericano de Pediatria, Confederacion Sudamericano de Sociedades de Pediatria

President: Prof. Carlos Prado.
Vice-President: Dr. Marcelo Garcia.
General Secretary: Dr. Alvaro Aguiar.
Place: Avenida mem de Sá 197, Rio de Janeiro. Meeting held Aug. 1-7, 1954.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 16 rue du Mont Blanc, Geneva, Switzerland.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. Bernard Laski, Toronto.
Secretary: Dr. Crawford Anglin, Toronto.
Place: Academy of Medicine.

Asociación de Pediatrias Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. P. A. Earnshaw, Ballow Chambers, Wickham Terrace, Brisbane. B17.
Honorary Secretary-Treasurer: Dr. D. C. Jackson, 217 Wickham Terrace, Brisbane. B17.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. Stanley Graham.
Honorary Secretary: Dr. Reginald Lightwood, Paediatric Unit, St. Mary's Hospital Medical School, London, W. C. 2.
Honorary Secretary: Dr. Philip Evans, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere. Time: Between Easter and Whitsunday.

Canadian Paediatric Society

President: Dr. G. R. Gayman, 710 Seymour St., Vancouver 2, B. C.
Secretary-Treasurer: Dr. J. C. Rathbun, 526 Waterloo St., London, Ont.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital, Fûglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital, Martinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Departamento de Pediatria da Associação Paulista de Medicina

President: Dr. J. Leme da Fonseca.
Secretary: Dr. Joaquim da Costa Marques.

Departamento de Puericultura e Pediatria da Associação Medica do Parana

President: Dr. Haroldo Beltrao.
Secretary: Dr. Mucio de Abreu Neto.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. Dr. med. W. Keller, Freiburg/Brsg., Universitätskinderklinik.
Secretary: Prof. Dr. med. J. Jochims, Lübeck, Städtische Kinderklinik.
Place: Freiburg/Brsg. Time: September, 1955.

Hellenic Society of Pediatrics

President: Dr. A. Androutselli.
Honorary Secretary: Dr. A. Inglessi, 4 Milioni St., Athens.
Place: Lecture Theater, University of Athens. Time: Last Tuesday of each month, 7 p. m.

Israel Pediatric Society

Chairman: Prof. Sh. Rosenbaum, 26 Bialik St., Tel Aviv.
Secretary: Dr. R. Kochmann, 131 Ben Jehuda Rd., Tel Aviv.
Place: Tel Aviv. Time: April 20-22, 1955.

Melbourne Paediatric Society

President: Dr. H. McLorinan.
Honorary Secretary: Dr. John H. Colebatch, 12 Collins St., Melbourne.
Place: Royal Children's Hospital, Melbourne. Time: Once monthly, February to December.

Nederlandse Vereeniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Roald Rinvik, Children's Department, Ullevål Hospital, Oslo.
Secretary: Dr. Bjarne Andersen, Children's Department, Ullevål Hospital, Oslo.
Time: Friday, six times a year.

Pediatric Society of New Zealand

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.

Philippine Pediatric Society

President: Dr. Renato Ma. Guerrero.
Secretary: Dr. Felix A. Estrada.
Place: Santo Tomas University Hospital and other pediatric centers. Time: Every two months.

Royal Society of Medicine, Section of Paediatrics

President: G. H. Macnab, F.R.C.S.
Honorary Secretaries: Ursula James, M.R.C.P., and Leslie Scott, M.D.
Sectional Editor: D. MacCarthy, M.D.
Place: 1 Wimpole St., London W.1 (Correspondence for these honorary officers should be sent to this address). Time: Fourth Friday of each month, 4:15 p.m.

Schweizerische Gesellschaft für Pädiatrie

President: P. D. Dr. F. Bamatter, St.-Léger 8, Genève.
Secretary: Dr. M. Nicod, Place Bel-Air 2, Lausanne.

Sociedad Argentinade Pediatrie

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviano de Pediatria

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedade Brasiliera de Pediatria

For officers, see IV° Congreso Sudamericano de Pediatria, above.

Sociedad Chihuahuense de Pediatría

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatria

President: Dr. Jorge Camacho Gamba.
Vice-President: Dr. Antonio Alvarez Riaño.
Secretary: Dr. Hernando Vanegas A.
Treasurer: Dr. Efrain Perry Villate.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos y Gonzales.
Secretary: Dr. Carlos Hernandez Miyares, Apartado 2430, Habana.
Place: Catedra de Clinica Infantil Hospital Nuestra Senora de las Mercedes and Hospital Municipal de Infancia, Habana. Time: 9 p.m., last Wednesday of every month.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional Concepción. Time: 7:30 p.m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litord

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatria y Puericultura del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Hernando Barrios-Angulo.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Pernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade de Puericultura e Pediatria do Maranbão

President: Dr. Odorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Sociedade Mineira de Pediatria

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

Sociedade Portugesa de Pediatria

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary-General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

Sociedad Uruguaya de Pediatria

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. H. Arroyo Parejo.
Vice-President: Dr. Manuel M. Lander.
Secretary: Dr. Guillermo Tovar E., P. O. Box 3122, Caracas.
Treasurer: Dr. Carlos Lares Compos.
Place: Hospital Municipal de Niños "J. M. de los Ríos," Caracas. Time: Once a month.

Sociedad Yucateca de Pediatria

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

La Société de Pédiatrie de Montréal

President: Dr. Henri Charbonneau, 3095 Cherbrooke, Montréal.
Secretary: Dr. Edmond Baril, 301 Carré St-Louis, Apt. 1, Montréal.
Time: Second Thursday of each month.

Société de Pédiatrie de Paris

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.
Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.
Place: Hôpital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p.m., third Tuesday of each month.

Société de Pédiatrie de Québec

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.
Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.
Place: Quebec. Time: May and November.

South African Paediatric Association

Chairman: Dr. H. L. Wallace, Durban.
Honorary Secretary-Treasurer: Dr. F. Walt, 126 Trust Bulidings, Gardiner St., Durban.

Swedish Association of Pediatrics

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Docent Justus, Ström, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm. Time: Second Friday of each month, except summer.

UNITED STATES

National

American Medical Association, Section on Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia 1. S. C.
Vice-Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit 2.

American Academy of Pediatrics

President: Dr. Crawford Bost, 115 Terrace Dr., San Francisco 27.
Vice-President: Dr. Harry Bakwin, 132 E. 71st St., New York 21.
Executive Secretary: Dr. E. H. Christopherson, 610 Church St., Evanston, Ill.
Treasurer: Dr. Edgar E. Martmer, 693 Washington Rd., Grosse Point 30, Mich.

Society for Pediatric Research

President: Dr. Russell Blattner.
Vice-President: Dr. Harold E. Harrison.
Secretary-Treasurer: Dr. Sydney S. Gellis, Boston.

The American Pediatric Society

President: Dr. Alfred H. Washburn, 2257 Ash St., Denver 7.
Vice-President: Dr. Amos U. Christie, Vanderbilt Hospital, Nashville 4, Tenn.
Secretary-Treasurer: Dr. Aims C. McGuinness, 1427 I St., N. W., Washington 5, D. C.
Place: Chateau Frontenac, Quebec. Time: June 15-18, 1955 (to be held in conjunction with the Society for Pediatric Research, the Canadian Paediatric Society, and the British Paediatric Association).

Sectional

Intermountain Pediatric Society

President: Dr. John T. Mason.
Secretary: Dr. Stanley R. Child.
Place: Ambassador Athletic Club, Salt Lake City. Time: 7 p.m.

New England Pediatric Society

President: Dr. Reuben C. Bates, 122 Waterman St., Providence, R. I.
Vice-President (President-Elect): Dr. Louis K. Diamond, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston, except Spring meeting. Time: Wednesdays, four times a year.

North Pacific Pediatric Society

President: Dr. Carl Ashley, 2455 N. W. Marshall St., Portland, Ore.
Secretary-Treasurer: Dr. S. Gorham Babson, 1107 S. W. 13th St., Portland, Ore.

Northwestern Pediatric Society

President: Dr. Stephen D. Mills, Dept. of Pediatrics, Mayo Clinic, Rochester, Minn.
Vice-President: Dr. A. J. Quellette, 1530 Larpenteur Ave., St. Paul, Minn.
Secretary-Treasurer: Dr. T. C. Papermaster, 215 Doctors' Bldg., Minneapolis.
Place: Minneapolis; St. Paul; Duluth, Minn., and Rochester, Minn. Time: January, April, July, and October.

Rocky Mountain Pediatric Society

President: Dr. Edwin Williams.
Vice-President: Dr. Oliver K. Scott.
Secretary-Treasurer: Dr. John H. Githens, Denver.

Southwestern Pediatric Society

President: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Carl A. Erickson, 960 E. Green St., Pasadena, Calif.
Place: Jonathan Club of Los Angeles. Time: 6:30 p.m., second Wednesday in January, March, May, September, and November.

Western Society for Pediatric Research

President: Dr. John Anderson.
Vice-President: Dr. Robert Aldrich.
Secretary-Treasurer: Dr. Forrest Adams.

State

Alabama Pediatric Society

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.
Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.
Place: Montgomery.

Arizona Pediatric Society

President: Dr. Henry E. Running.
Secretary. Dr. William F. Schaffman.
Time: On Call.

California Medical Association, Section on Pediatrics

Chairman: Dr. Joseph W. St. Geme, 511 S. Bonnie Brae, Los Angeles 5.
Secretary: Dr. Alvin H. Jacobs, 2201 Webster St., San Francisco 15.
Assistant Secretary: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills.

Florida State Pediatric Society

President: Dr. Charlotte C. Maguire, 1413 Kuhl Ave., Maguire Bldg., Orlando
Secretary-Treasurer: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.

Georgia Pediatric Society

President: Dr. John A. Simpson, Athens.
Secretary: Dr. J. Harry Lange, 490 Peachtree St., Atlanta.
Place: Savannah. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Louis Spekter, Division of Crippled Children, Department of Health, State ot Connecticut, Hartford.
Secretary: Dr. Frank E. Roth, 179 Allyn St., Hartford.
Time: With the Connecticut State Medical Society in the spring, with the Connecticut State Clinical Congress in the fall; winter meeting usually in December.

Illinois State Medical Society, Section on Pediatrics

Chairman: Howard R. Miller, 418 Jefferson Bldg., Peoria 2.
Secretary: Harry H. Boyle, 2376 E. 71st St., Chicago 49.

Indiana State Pediatric Society

President: Dr. Harold D. Lynch, Evansville.
Secretary: Dr. L. T. Meiks, Indianapolis.

Iowa Pediatric Society

President: Dr. P. E. Gibson, 1503 Brady St., Davenport.
Vice-President: Dr. Arlan F. Harrington, 924 M. N. B. Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting. Fall meeting in Sept., at University Hospital, Pediatric Dept., Iowa City.

Kentucky Pediatric Society

President: Dr. Margaret Limper, Louisville.
Secretary-Treasurer: Dr. Selby V. Love, Louisville.
Place: Louisville. Time: Spring.

Louisiana State Pediatric Society

President: Dr. Jack E. Strange, 3439 Prytania, New Orleans.
Vice-President: Dr. Charles E. Anderson, 1560 Line, Shreveport.
Secretary: Dr. Joseph M. Perret Jr., 2329 S. Carrollton, New Orleans.
Treasurer: Dr. William C. Rivenbark, 1448 Louisiana Ave., New Orleans.
Place: New Orleans. Time: May.

Massachusetts Hospital Association

President: Dr. Philip D. Bonnet, Administrator, Massachusetts Memorial Hospitals, Boston.
Executive Secretary: Henry G. Brickman, 14 Somerset St., Boston 8.

Michigan State Medical Society, Pediatric Section

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary: Dr. Park S. Bradshaw, 1014 Jefferson St., Muskegon.

Montana Pediatric Society

President: Dr. Orville M. Moore, 555 Fuller Ave., Helena.
Secretary: Dr. Joseph W. Brinkley, 410 Central Ave., Great Falls.
Place: Variable. Time: Spring and fall.

Nebraska Pediatric Society

President: Dr. Paul Bandroft, Lincoln.
Vice-President: Dr. Charles Tompkins.
Secretary-Treasurer: Dr. A. J. Lombardo, 401 Aquila Ct., Omaha.
Place: Children's Memorial Hospital. Time: 6 p.m., dinner, third Thursday of each month.

New Hampshire Pediatric Society

President: Dr. Mac Lean J. Gill, 1 South St., Concord.
Secretary-Treasurer: Dr. Robert F. Wilson, 113 Locust St., Dover.
Place: Alternately Concord, Hanover, Laconia, and Manchester. Time: Four times a year.

New Mexico Pediatric Society

President: Dr. M. K. Wylder, Suite 14, Medical Arts Sq., Albuquerque.
Secretary: Dr. Ly Werner, Suite 25, Medical Arts Sq., Albuquerque.
Place: Variable. Time: Every two or three months.

North Carolina Pediatric Society

President: Dr. Robert A. Moore, 1505 Elizabeth Ave., Charlotte 4.
Secretary: Dr. Fred R. Cochrane Jr., 1361 E. Morehead St., Charlotte.
Place: Pinehurst. Time: May 3, 1955.

South Carolina Pediatric Society

President: Dr. Walter Moore Hart, 117 W. Cheves St., Florence.
Secretary: Dr. John R. Paul Jr., 82 Rutledge Ave., Charleston.
Place: Columbia, S. C. Time: Second Monday and Tuesday in September.

Tennessee Pediatric Society

President: Dr. O. L. Von Canon, 846 McCallie Ave., Chattanooga.
Secretary: Dr. Oliver W. Hill, 4807 Newcom Ave., Knoxville.

Texas Pediatric Society

President: Dr. M. C. Carlisle, Waco.
President-Elect: Dr. Russell Blattner, Houston.
Secretary: Dr. James N. Walker, Fort Worth.
Treasurer: Dr. Jack M. Woodall, Big Springs.

Virginia Pediatric Society

President: Dr. T. J. Humphries, Roanoke.
Vice-President: Dr. F. R. Hopkins, Lynchburg.
Secretary-Treasurer: Dr. A. P. Booker, Charlottesville.

WISCONSIN STATE MEDICAL SOCIETY, SECTION OF PEDIATRICS

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p.m., October, December, February, and March.

AKRON PEDIATRIC SOCIETY

President: Dr. Joseph M. Ulrich.
Vice-President: Dr. Lewis E. Rector.
Secretary-Treasurer: Dr. Max E. Griffin.
Time: Quarterly.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

President: Dr. Wilson Grubb, 4 E. 33d St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.
Place: 1211 Cathedral St., Baltimore 1. Time: 8:30 p.m., second Tuesday in November, January, and March.

BRONX PEDIATRIC SOCIETY

President: Dr. M. H. Grand, 1749 Grand Concourse, New York.
Secretary: Dr. Charles T. Fried, 1220 Grand Concourse, New York.
Place: Morrisania City Hospital. Time: 8:30 p.m., second Wednesday of each month, except June, July, August, and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Joseph Battaglia, 713 Bushwick Ave.
Secretary: Dr. A. H. Emerson, 7721 Ridge Blvd.
Place: Granada Hotel, Brooklyn. Time: 8:45 p.m., fourth Wednesday of February, March, April, October, and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold.
Secretary: Dr. Richard A. Downey.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p.m., first Monday of each month, September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Williams, 58 Swan St. S., Albany.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.
Place: Various cities in New York State; fall meeting jointly with Upper New York State Academy of Pediatrics. Time: Third Tuesday of April and October.

CENTRAL OHIO PEDIATRIC SOCIETY

President: Dr. O. W. Hosterman, 350 East Broad St., Columbus 15.
Secretary-Treasurer: Dr. John Riepenhoff, 2998 Sullivant Ave., Columbus.
Place: As announced. Time: Third Wednesday of September, November, January, March, and May.

Chicago Pediatric Society

President: Dr. Eugene T. McEnery.
Vice-President: Dr. Maxwell P. Borovsky.
Secretary: Dr. Ralph H. Kunstadter, 104 S. Michigan Blvd.
Treasurer: Dr. Noel G. Shaw.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. John E. Allen, 3402 Clifton Ave.
Vice-President: Dr. Robert A. Lyon, Children's Hospital.
Secretary-Treasurer: Dr. William D. De Vaux, 7373 Brookcrest Ave.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. C. Lewis Concklin, 2205 16th St.
Secretary-Treasurer: Dr. Sam Powell, 301 Palmero.
Place: La Louisiane Restaurant. Time: 7:30 p.m., last Wednesday of January, March, May, July, September, and November.

Dade County Pediatric Society

President: Dr. Lynn Whelchel, DuPont Bldg., Miami, Fla.
Secretary: Dr. Howard Engle, 311 Lincoln Rd., Miami Beach, Fla.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.
Place: Children's Hospital of Texas. Time: 6:30 p.m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Wolf Zuelzer.
Secretary: Dr. Mario S. Cioffari.
Place: Variable. Time: Five times a year.

Honolulu Pediatric Society

President: Dr. John Peyton, Medical Group, 1133 Punchbowl St.
Recording Secretary: Goonzo Yamashita, 1618 S. King St.
Corresponding Secretary-Treasurer: Dr. H. M. Sexton, Straub Clinic, 1020 Kapiolani St.
Place: At doctors' homes in rotation. Time: 6 p.m., third Thursday of each month.

Houston Pediatric Society

President: Dr. David Schrum, 5101 Fannin St., Houston.
Secretary: Dr. Juanita Thacker Hart, 306 South 7th St., Bellaire.
Place: River Oaks Country Club. Time: 6:30 p.m., fourth Tuesday of each month.

Kansas City Southwest Pediatric Society

President: Dr. Frank Houge, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.
Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.
Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Robert Shirley, 133 S. Lasky Dr., Beverly Hills, Calif.
Vice-President: Dr. Deron Housepian, 960 E. Green St., Pasadena, Calif.
Secretary: Dr. Margaret Jones, 405 Hilgard Ave., University of California School of Medicine at Los Angeles, Los Angeles 24.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd., Los Angeles. Time: Second Thursday of alternate months beginning in September.

Louisville Pediatric Society

President: Dr. Harry S. Andrews.
Vice-President: Dr. Joseph Little.
Secretary-Treasurer: Dr. Kenneth P. Crawford.
Place: Variable. Time: Five times a year, as announced.

Medical Society of the County of Kings and Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn.
Secretary: Dr. Bernard Greenberg, 755 Ocean Ave., Brooklyn 26.
Treasurer: Dr. David Dragutsky, 1466 49th St., Brooklyn.
Place: Kings County Medical Society Auditorium, 1313 Bedford Ave., Brooklyn. Time: 8:45 p.m., fourth Monday of January, March, April, October, and November.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington 20.
Secretary: Dr. John E. Cassidy, 5402 Connecticut Ave. N.W., Washington.
Place: Medical Society Bldg., 1718 M St. N. W., Washington. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. Clifton W. Woolley, 2448 Poplar Ave.
Vice-President: Dr. Steve H. Turnbull, 848 Adams.
Secretary-Treasurer: Dr. Charles H. Householder, 321 S. Bellevue.
Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. Kenneth Winters, Wauwatosa, Wis.
Secretary: Dr. James P. Conway, Milwaukee.
Place: Milwaukee University Club. Time: Second Wednesday of February, April, June, and October.

Mobile Pediatric Society

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.
Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

Nashville Pediatric Society

President: Dr. Thomas Weaver, Bennie Dillon Bldg., Nashville, Tenn.
Secretary: Dr. Ethel Walker, 3415 West End Ave., Nashville, Tenn.
Place: Homes of members. Time: Third Thursday of every month.

Nassau Pediatric Society

President: Dr. Mildred Wicker Jackson, 254 South St., Oyster Bay, N. Y.
Secretary-Treasurer: Dr. David J. Posner, 98 Wolcott Rd., Levittown, N. Y.
Place: Felice's, Post Ave., Westbury, N. Y. Time: 7:30 p.m., second Monday of October, December, February, April, and June.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Jerome L. Kohn, 50 W. 96th St., New York 25.
Secretary: Dr. Lawrence B. Slobody, 1 E. 105th St., New York 12.
Place: New York Academy of Medicine, 2 E. 103d St. Time: 8:30 p.m., second Thursday of each month, November to May, inclusive.

Northern California Pediatric Society

President: Dr. Edward Campion, 707 C St., San Rafael.
Secretary-Treasurer: Dr. Joseph H. Davis, 300 Homer Ave., Palo Alto.
Place: San Francisco. Time: Quarterly, as speakers are available.

Oklahoma City Pediatric Society

President: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Louis Frank, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. Norman Kendall, 3401 N. Broad St., Philadelphia 40.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Christian John Stoecklein, 519 Medical Arts Bldg., Pittsburgh 13.
Secretary-Treasurer: Dr. James W. Stirling, 694 Lincoln Ave., Pittsburgh 2.
Place: Western State Psychiatric Institute and Clinic. Time: Second Friday in October, December, February, and April.

Queens Pediatric Society

President: Dr. Moe Goldstein, 111-32 76th Ave., Forest Hills, N. Y.
Secretary: Dr. John Finnegan, 36-19 Bowne St., Flushing, N. Y.
Place: Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.
Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

San Antonio Pediatric Society

President: Dr. Philip Magrish, 402 Fulton Ave.
Secretary: Dr. Jack M. Wright, 403 Summit Ave.
Time: 7:30 p.m., supper, first Tuesday of each month.

St. Louis Pediatric Society

President: Dr. H. E. Wachter, 8505 Delmar.
Vice-President: Dr. Raymond J. LaDriere, 35 No. Central, Clayton 5, Mo.
Secretary-Treasurer: Dr. Leo F. Gowen, 337 W. Lockwood, Webster Groves 19, Mo.
Place: Medart's Restaurant. Time: 7 p.m., second Thursday of each month from September to May, inclusive.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.
Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara, Calif.
Place: Varies. Time: Two to three times yearly, on call.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Fred J. Chapin, 101 John St., Bay City.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.
Place: University Hospital, Ann Arbor.

Waco Pediatric Society

President: Dr. Jack Flowers.
Secretary: Dr. F. W. Hoehn.
Place: 1918 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

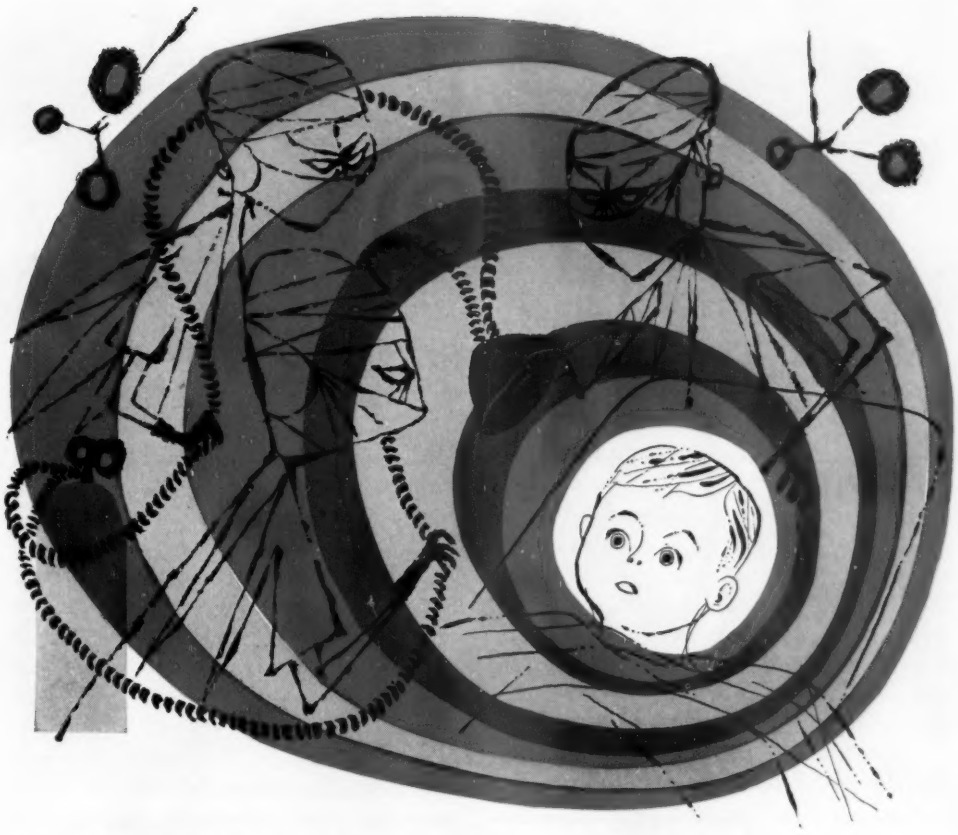
Chairman: Dr. Donald R. Reed, 14 S. Broadway, Irvington, N. Y.
Secretary: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Four dinner meetings a year, November, February, April, and June.

Western Michigan Pediatric Society

President: Dr. A. Morgan Hill, 310 Fulton, E., Grand Rapids.
Secretary: Dr. John C. Montgomery, 1810 Wealthy St., S.E., Grand Rapids.
Place: Two meetings in Grand Rapids, two elsewhere. Time: First Wednesday of October, November, April, and May.

Wichita Pediatric Society

President: Dr. Frank L. Menehan.
Secretary: Dr. R. C. Knappenberger.
Place: Homes of members. Time: 8:30 p.m., first Thursday, October through May.



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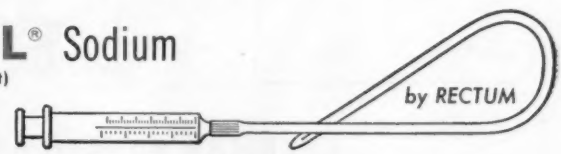

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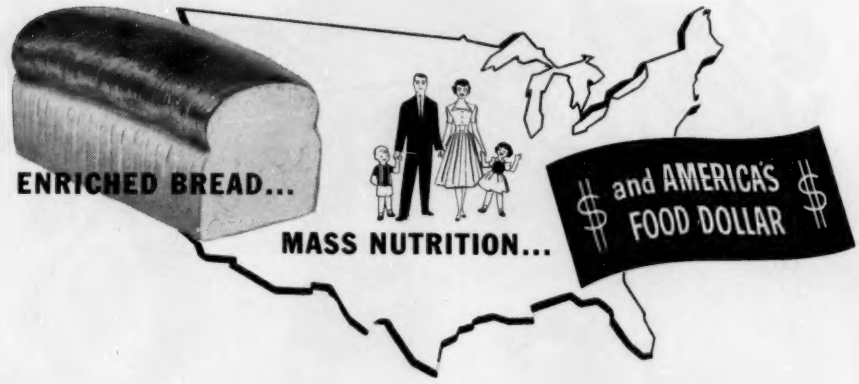

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Column I of the appended table shows the amounts of nutrients and nutrient energy provided by 5½ ounces of enriched bread. Column II gives the percentages of the recommended daily dietary allowance[4] available from this amount of enriched bread.

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Niacin	3.4 mg.	24%
Riboflavin	0.23 mg.	14%
Iron	4.1 mg.	34%
Calcium (average)	137 mg.	17%
Calories	418	14%

It is evident that enriched bread furnishes substantially more than its share of most nutrients. Thus it compensates for deficiencies of these nutrients in other foods of the everyday diet. Since virtually all enriched bread is made with nonfat milk solids, its protein—containing an average of 10.5 per cent milk protein and 89.5 per cent wheat and yeast proteins[5]—functions for growth as well as tissue maintenance.

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1. Bureau of Labor Statistics, United States Department of Labor, Jan., 1954.
2. Sebrell, W.H.: Trends and Needs in Nutrition, J.A.M.A. *152:*42 (May 2) 1953.
3. Council on Foods and Nutrition, American Medical Association: A Statement of General Policy Concerning the Addition of Specific Nutrients to Foods, J.A.M.A. *154:*145 (Jan. 9) 1954.
4. Shank, R.E.: Revisions of the Recommended Dietary Allowances, J. Am. Dietet. A. *30:*105 (Feb.) 1954.
5. Sherman, H.C.: Chemistry of Food and Nutrition, ed. 8, New York, The Macmillan Co., 1952, pp. 212, 599.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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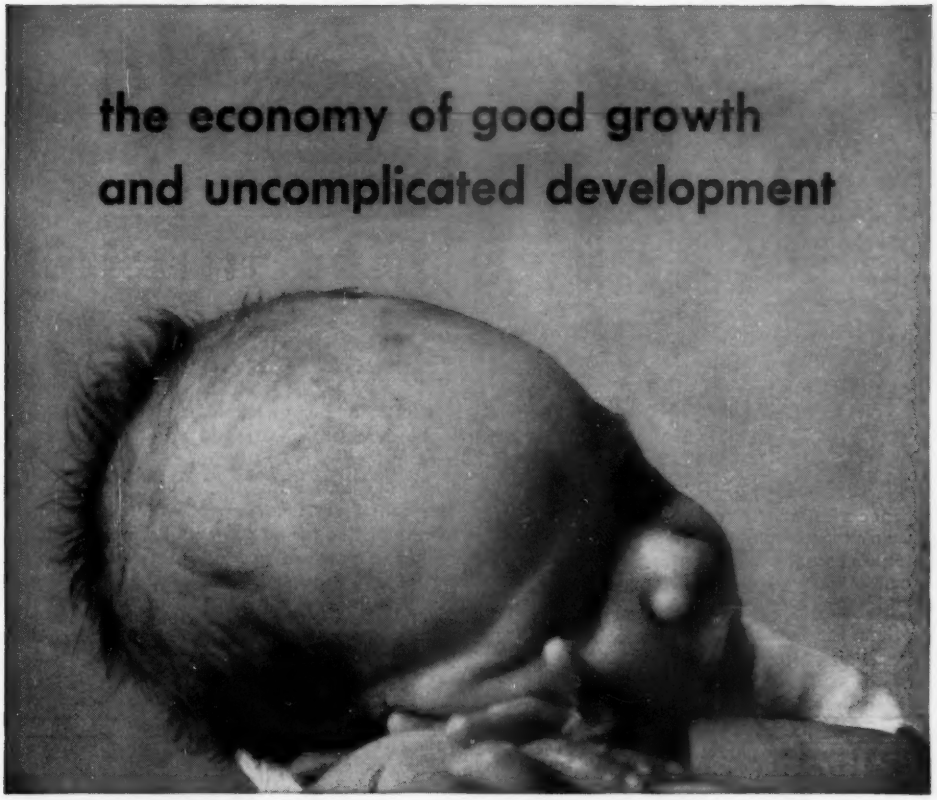

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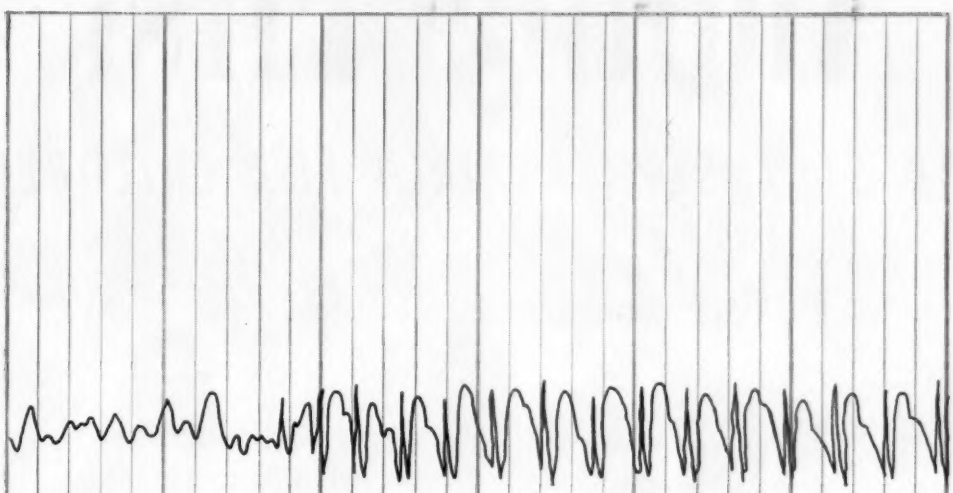

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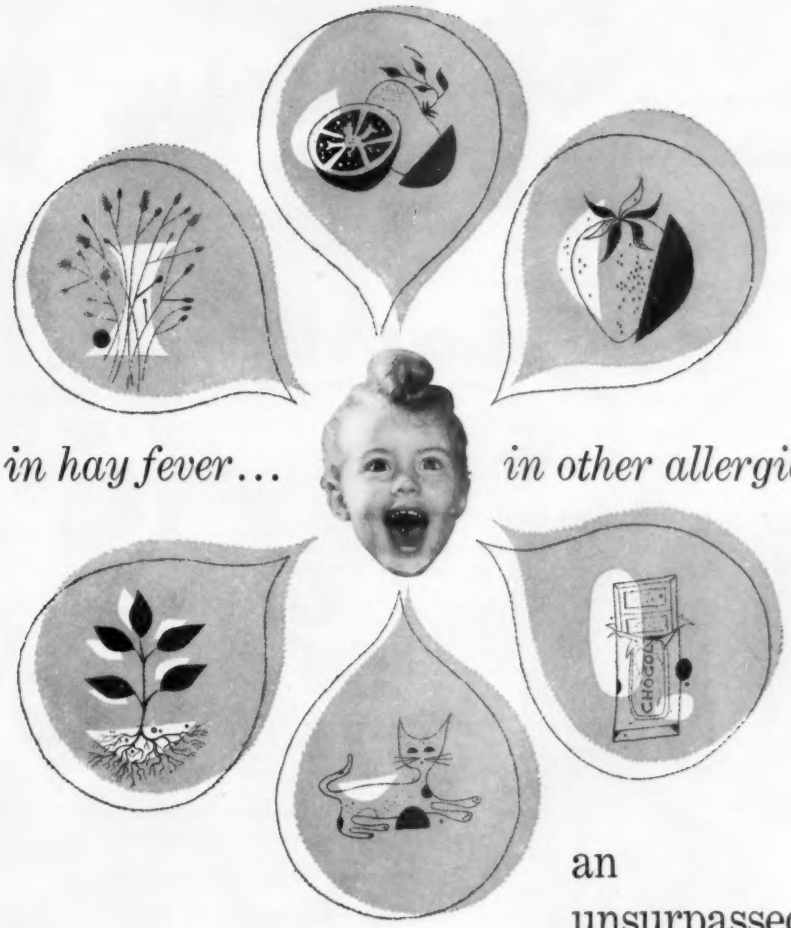

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Pyribenzamine® Elixir

A palatable, spice-flavored antihistamine, Pyribenzamine Elixir offers highly effective therapy in a broad range of allergies. *Dosage can be readily adjusted* to any age, any individual requirement. *Prescribe this well-accepted medication* alone or as a therapeutic vehicle. Each 4-ml. teaspoonful contains 30 mg. Pyribenzamine citrate.

Pyribenzamine® citrate (tripelennamine citrate CIBA)

CIBA
SUMMIT, N. J.

2/2097M

you provide
nutritional safeguards
at every feeding
when you prescribe

Lactum

Liquid or Powdered

nutritionally sound formula for infants

An extra protein margin of safety for better tissue structure—optimal growth

20 Gm. protein	16 Gm. protein
Lactum® formula for a 10-lb. infant	Recommended Daily Allowance for a 10-lb. infant

a protein margin of safety...plus

1. All the natural nutrients of whole milk.
2. Natural butterfat retained; no animal or vegetable fats substituted; perfectly homogenized.
3. Twice as much vitamin B_6 as breast milk.
4. Added Dextri-Maltose® permits gradual, spaced absorption; spares protein and helps metabolize fat.
5. Caloric distribution based on authoritative recommendations.
6. Curd tension practically zero, for exceptional digestibility.
7. Good height-weight curves, firm tissue structure, excellent blood pictures.
8. Stools normally soft, light-colored, without offensive odor.
9. Notable absence of undue hunger, regurgitation.
10. Both Liquid Lactum® and Powdered Lactum offer the maximum in convenience. They mix easily with water to make uniform formulas.

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it ventilates . . .

because it affects diaphragm and intercostals . . . both! . . .

- A.M.A. Council accepted.
- Respiratory rate instantly adjustable, clearly indicated.
- Applies positive or negative pressures, or both.
- No chafing, constricting "air seals," maximum patient comfort.
- No oppressive weight on patient . . . cuirass independently supported on bed.
- Covers anterior torso only . . . patient's extremities freely accessible for nursing care or therapy.
- Tracheotomy area always free.
- Instant changeover to manual operation if power fails.

SALIENT among the many virtues of the Technicon-Huxley Respirator is the amplitude of ventilation it provides for a non-confining apparatus. Because it affects the entire anterior torso, with pressure brought to bear *on both* diaphragm and intercostals, it achieves a new degree of ventilating efficiency hitherto thought visionary with a compact, lightweight apparatus.

That is why it has so completely captured the imagination of those who have seen it working . . . why, in the few short months since its introduction, it is already being widely used. Word gets around fast when anything so badly needed so ably fills the need!

Perhaps you haven't seen the Technicon-Huxley Respirator in actual operation. Our concise descriptive brochure is the next best thing. It's yours for the asking. Write

CONITECH, LTD.
Chauncey, New York

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technicon-huxley®
chest-abdomen respirator

PATENTED

For Nasal
Congestion in Children
The vasoconstrictive and decongestant action of Neo-Synephrine rapidly relieves nasal congestion in children—due to colds, sinusitis, or allergic rhinitis.
Administered by the new handy spray—plastic squeeze bottle—or the standard dropper method, Neo-Synephrine reduces the engorgement of the nasal mucosa promptly and with virtual freedom from irritation. Normal drainage and aeration are restored, making it possible for the child to sleep normally, and for the infant to feed and rest. Neo-Synephrine also helps to forestall the development of more serious chronic complications of upper respiratory tract infections.
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NEO-SYNEPHRINE®
Hydrochloride
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